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(54) Title: METH1 AND METH2 POLYNUCLEOTIDES AND POLYPEPTIDES

(57) Abstract

The present invention relates to novel anti-angiogenic proteins, related to thrombospondin. More specifically, isolated nucleic acid molecules are provided encoding human METH1 and METH2. METH1 and METH2 polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. Also provided are diagnostic methods for the prognosis of cancer and therapeutic methods for treating individuals in need of an increased amount of METH1 or METH2.

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METH1 and METH2 Polynucleotides and Polypeptides

Background of the Invention

Federally-Sponsored Research and Development

Part of the work performed during development of this invention utilized U.S. Government funds. The U.S. Government has certain rights in this invention.

Field of the Invention

The present invention relates to novel anti-angiogenic proteins, related to thrombospondin. More specifically, isolated nucleic acid molecules are provided encoding human METH1 and METH2 (ME, for metalloprotease, and TH, for thrombospondin). METH1 and METH2 polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. Also provided are diagnostic methods for the prognosis of cancer and therapeutic methods for treating individuals in need of an increased amount of METH1 or METH2.

Related Art

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a tightly regulated process in normal adults. Under physiological circumstances, growth of new capillaries is tightly controlled by an interplay of growth regulatory proteins which act either to stimulate or to inhibit blood vessel growth. Normally, the balance between these forces is tipped in favor of inhibition and consequently blood vessel growth is restrained. Under certain pathological circumstances, however, local inhibitory controls are unable to restrain the increased activity of angiogenic inducers. Angiogenesis is a key step in the metastasis of cancer (Folkman, *Nature Med. 1*:27-31 (1995)) and in abnormal wound healing, inflammation, rheumatoid arthritis, psoriasis, and diabetic retinopathy, it is integral to the pathology (Folkman *et al.*, *Science 235*:442-447 (1987)), engendering the hope that these pathological entities could be regulated

by pharmacological and/or genetic suppression of blood vessel growth (Iruela-Arispe *et al.*, *Thromb. Haem. 78*:672-677 1997)).

Thrombospondin-1 (TSP-1) is a 450 kDa, anti-angiogenic adhesive glycoprotein released from activated platelets and secreted by growing cells (reviewed in Adams, *Int. J. Biochem. Cell. Biol.* 29:861-865 (1997)). TSP-1 is a homotrimer, with each subunit comprised of a 1152 amino acid residue polypeptide, post-translationally modified by *N*-linked glycosylation and beta-hydroxylation of asparagine residues.

TSP-1 protein and mRNA levels are regulated by a variety of factors. TSP-1 protein levels are downregulated by IL-1 alpha and TNF alpha. TSP-1 mRNA and protein levels are upregulated by polypeptide growth factors including PDGF, TGF-beta, and bFGF (Bornstein, *Faseb J. 6*: 3290-3299 (1992)) and are also regulated by the level of expression of the p53 tumor suppressor gene product (Dameron *et al.*, *Science 265*:1582-1584 (1994)). At least four other members of the thrombospondin family have been identified: TSP-2, TSP-3, TSP-4, and TSP-5 (also called COMP). There is a need in the art to identify other molecules involved in the regulation of angiogenesis.

Summary of the Invention

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the METH1 polypeptide having the amino acid sequence shown in SEQ ID NO:2 or the amino acid sequence encoded by the cDNA clone deposited in a bacterial host as ATCC Deposit Number 209581 on January 15, 1998.

The present invention also provides isolated nucleic acid molecules comprising a polynucleotide encoding the METH2 polypeptide having the amino acid sequence shown in SEQ ID NO:4 or the amino acid sequence encoded by the cDNA clone deposited in a bacterial host as ATCC Deposit Number 209582 on January 15, 1998.

The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them for production of METH1 or METH2 polypeptides or peptides by recombinant techniques.

The invention further provides an isolated METH1 or METH2 polypeptide having an amino acid sequence encoded by a polynucleotide described herein.

The invention further provides a diagnostic method useful during diagnosis or prognosis of cancer.

An additional aspect of the invention is related to a method for treating an individual in need of an increased level of METH1 or METH2 activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an isolated METH1 or METH2 polypeptide of the invention or an agonist thereof.

Brief Description of the Figures

Figure 1 shows the nucleotide (SEQ ID NO:1) and deduced amino acid (SEQ ID NO:2) sequences of METH1. The protein has a predicted leader sequence of about 28 amino acid residues (underlined).

Figure 2 shows the nucleotide (SEQ ID NO:3) and deduced amino acid (SEQ ID NO:4) sequences of METH2. The protein has a predicted leader sequence of about 23 amino acid residues (underlined).

Figure 3 shows a comparison of the amino acid sequence of METH1 (SEQ ID NO:2) and METH2 (SEQ ID NO:4) with that of their closest homologue, a bovine metalloprotease (pNPI) (SEQ ID NO:5). Identical amino acids are boxed. Functional domains predicted by sequence and structural homology are labeled, including the signal peptide (single line), the potential cleavage site for mammalian subtilisin (double underlined), the zinc-binding-site (dotted line) in the metalloprotease domain, and the putative disintegrin loops (arrows).

Figure 4 shows the primary structure of METH1, METH2 and pNPI which includes a prodomain, a catalytic metalloprotease domain, a cysteine rich disintegrin domain, a TSP-like domain, a spacer region and a different number of TSP-like domains, three for METH1, two for METH2, and four for pNPI.

Figure 5 shows a comparison of the TSP-like domain of METH1 (SEQ ID NO:2) and METH2 (SEQ ID NO:4) with those of TSP1 (SEQ ID NOs:6, 7, and 8) and TSP2 (SEQ ID NOs:9, 10, and 11), cysteines are numbered 1 to 6, tryptophans are marked by asterisks.

Figure 6 shows that peptides and recombinant protein derived from the TSP-like domain of METH1 and METH2 block VEGF-induced angiogenesis. Angiogenesis was induced on CAMs from 12-14-day-old embryos using a nylon mesh containing VEGF casted on matrigel and in the presence or absence of the peptides or recombinant protein. Capillary density was evaluated as described in Example 4. Positive and negative control included VEGF alone and vehicle alone, respectively. (A) Quantification of the angiogenic response induced by VEGF in the presence of recombinant proteins. TSP1, purified platelet TSP1, GST, purified GST, GST-TSP1, GST-METH1, and GST-METH2 are described in Example 4. (B) Quantification of the angiogenic response induced by VEGF in the presence or absence of the peptides; P-TSP1, P-METH1, and P-METH2 (peptide derived from the Type I repeats of TSP, METH1 and METH2, respectively); SC1 and SC2 are scramble peptides used as controls. (C) Dose-response of the VEGF-induced angiogenesis in the presence of GST-METH1. (D) Dose-response of the VEGF-induced angiogenesis in the presence of GST-METH2. The angiogenic index was expressed considering the vascular response from the VEGF-matrigel as 100% and subtracting the background levels (matrigel alone). Assays were repeated, at least, twice. Each treatment was done in triplicate. Values represent the mean, bars indicate standard deviations. *$p<0.001$.

Figure 7 shows the effect of METH1 and METH2 recombinant proteins on bFGF-stimulated cell proliferation. Cells were cultured on 24-well plates in media containing bFGF and the recombinant protein to be tested (3 μg/ml, unless

indicated in the graph). Controls included vehicle or GST recombinant protein alone. (A), HDEC, human dermal endothelial cells; (B), HMEC, human mammary epithelial cells; (C), HDF, human dermal fibroblasts; (D), SMC, smooth muscle cells; (E) Dose-response of GST-METH1 and GST-METH2 on HDEC proliferation. Experiments were repeated, at least, twice. Each treatment was done in triplicate. Values represent the mean, bars indicate standard deviations. *$p<0.01$.

Figure 8 shows a schematic representation of the pHE4-5 expression vector (SEQ ID NO:12) and the subcloned METH1 or METH2 cDNA coding sequence. The locations of the kanamycin resistance marker gene, the METH1 or METH2 coding sequence, the oriC sequence, and the *lac*Iq coding sequence are indicated.

Figure 9 shows the nucleotide sequence of the regulatory elements of the pHE promoter (SEQ ID NO:13). The two *lac* operator sequences, the Shine-Delgarno sequence (S/D), and the terminal *Hind*III and *Nde*I restriction sites (italicized) are indicated.

Figure 10 shows an analysis of the METH1 amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the METH1 or METH2 protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. The domains defined by these graphs are contemplated by the present invention. Tabular representation of the data summarized graphically in Figure 10 can be found in Table 1.

Figure 11 shows an analysis of the METH2 amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic

regions of the METH1 or METH2 protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. The domains defined by these graphs are contemplated by the present invention. Tabular representation of the data summarized graphically in Figure 11 can be found in Table 2.

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Table 1

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Met	1	A	A	.	.	.	.	.	0.41	*	.	.	-0.30	0.60
Gly	2	.	A	.	.	.	.	C	0.91	*	.	.	0.50	0.81
Asn	3	A	A	.	.	.	.	.	0.71	*	.	.	0.75	1.24
Ala	4	A	A	.	.	.	.	.	0.89	*	.	.	1.09	1.26
Glu	5	A	A	.	.	.	.	.	0.93	*	.	F	1.58	1.97
Arg	6	.	A	B	.	.	.	.	1.23	.	.	F	1.92	1.21
Ala	7	.	.	B	.	.	T	.	1.69	.	.	F	2.66	1.61
Pro	8	.	.	.	.	T	T	.	1.39	.	.	F	3.40	1.82
Gly	9	.	.	.	.	T	T	.	1.28	.	.	F	3.06	1.25
Ser	10	.	.	.	.	T	T	.	0.93	.	.	F	2.42	1.07
Arg	11	.	.	.	.	T	T	.	0.61	.	*	F	1.93	0.68
Ser	12	.	.	.	.	T	T	.	0.34	*	.	F	1.74	1.07
Phe	13	.	.	B	.	.	T	.	0.34	*	.	F	0.25	0.59
Gly	14	.	.	B	.	.	T	.	0.38	*	.	F	0.25	0.47
Pro	15	.	.	B	B	.	.	.	-0.13	*	.	F	-0.45	0.50
Val	16	.	.	B	B	.	.	.	-1.06	*	.	F	-0.45	0.48
Pro	17	.	.	B	B	.	.	.	-1.57	.	.	F	-0.45	0.40
Thr	18	.	A	B	.	.	.	.	-1.68	.	.	F	-0.45	0.21
Leu	19	.	A	B	.	.	.	.	-1.92	.	.	.	-0.60	0.24
Leu	20	A	A	.	.	.	.	.	-2.30	.	.	.	-0.60	0.15
Leu	21	A	A	.	.	.	.	.	-2.03	.	.	.	-0.60	0.11

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	22	A	A	.	.	.	.	.	-2.63	.	.	.	-0.60	0.13
Ala	23	A	A	.	.	.	.	.	-3.13	.	.	.	-0.60	0.13
Ala	24	A	A	.	.	.	.	.	-2.91	.	.	.	-0.60	0.13
Ala	25	A	A	.	.	.	.	.	-2.96	.	.	.	-0.60	0.16
Leu	26	A	A	.	B	.	.	.	-2.44	.	.	.	-0.60	0.12
Leu	27	A	A	.	B	.	.	.	-1.63	.	.	.	-0.60	0.16
Ala	28	A	A	.	B	.	.	.	-1.63	.	.	.	-0.30	0.26
Val	29	A	A	.	B	.	.	.	-1.86	.	.	.	-0.30	0.32
Ser	30	A	A	.	.	.	.	.	-1.61	*	*	.	-0.30	0.32
Asp	31	A	A	.	.	.	.	.	-0.69	*	*	F	-0.15	0.31
Ala	32	A	A	.	.	.	.	.	-0.09		*	F	0.75	0.83
Leu	33	.	A	.	.	.	.	C	0.20	*	.	F	1.55	0.96
Gly	34	.	A	.	.	.	.	C	1.06	*	*	F	1.85	0.77
Arg	35	.	.	.	.	.	T	C	1.36	*	*	F	2.70	1.32
Pro	36	.	.	.	.	.	T	C	1.36	*	*	F	3.00	2.76
Ser	37	.	.	.	.	.	T	C	1.94	*	.	F	2.70	4.66
Glu	38	A	.	.	.	.	T	.	2.76	*	.	F	2.20	4.12
Glu	39	A	A	.	.	.	.	.	2.29	*	*	F	1.50	4.61
Asp	40	A	A	.	.	.	.	.	1.32	*	*	F	1.20	2.84
Glu	41	A	A	.	.	.	.	.	0.68	.	.	F	0.90	1.22
Glu	42	A	A	.	.	.	.	.	0.77	.	.	F	0.75	0.52
Leu	43	A	A	.	.	.	.	.	0.77	.	.	.	0.60	0.48

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Val	44	A	A	.	.	.	.	.	-0.04	.	.	.	0.60	0.48
Val	45	A	A	.	.	.	.	.	-0.04	*	.	.	-0.30	0.23
Pro	46	A	A	.	.	.	.	.	0.07	*	.	.	-0.30	0.48
Glu	47	A	.	.	.	.	.	.	-0.52	*	.	F	1.10	1.27
Leu	48	A	.	.	.	.	.	.	0.08	*	.	F	1.41	1.73
Glu	49	A	.	.	.	.	.	.	0.59	*	.	F	1.72	1.73
Arg	50	A	.	.	.	.	.	.	1.41	*	.	F	1.88	0.99
Ala	51	A	.	.	.	.	T	.	1.28	*	.	F	2.24	1.64
Pro	52	.	.	.	.	T	T	.	0.97	*	.	F	3.10	0.93
Gly	53	.	.	.	.	T	T	.	1.47	*	*	F	2.49	0.69
His	54	.	.	.	.	.	T	C	1.58	*	*	F	1.38	0.98
Gly	55	.	.	.	.	.	.	C	0.66	*	*	F	1.62	1.25
Thr	56	.	.	.	.	.	.	C	1.36	.	*	F	0.71	1.04
Thr	57	.	A	B	.	.	.	.	0.76	.	*	F	0.60	1.49
Arg	58	.	A	B	.	.	.	.	1.07	.	*	F	0.60	1.25
Leu	59	.	A	B	.	.	.	.	0.51	.	*	.	0.45	1.17
Arg	60	.	A	B	.	.	.	.	0.16	.	*	.	0.30	0.82
Leu	61	.	A	B	.	.	.	.	0.47	.	*	.	-0.30	0.36
His	62	.	A	B	.	.	.	.	0.78	.	*	.	-0.30	0.74
Ala	63	A	A	.	.	.	.	.	0.67	.	*	.	0.30	0.65
Phe	64	A	A	.	.	.	.	.	0.67	.	*	.	-0.15	1.37
Asp	65	A	A	.	.	.	.	.	0.56	.	*	F	-0.15	0.83

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gln	66	A	A	.	.	.	.	.	0.56	.	*	F	0.60	1.37
Gln	67	A	A	.	.	.	.	.	0.59	.	*	F	0.60	1.30
Leu	68	A	A	.	.	.	.	.	0.37	*	*	F	0.90	1.35
Asp	69	A	A	.	.	.	.	.	1.18	*	*	.	0.30	0.64
Leu	70	.	A	B	.	.	.	.	0.97	.	*	.	0.94	0.73
Glu	71	.	A	B	.	.	.	.	0.97	.	*	.	1.43	1.37
Leu	72	.	A	B	.	.	.	.	0.67	.	*	.	1.77	1.37
Arg	73	.	.	.	.	.	T	C	1.18	*	*	F	2.86	2.22
Pro	74	.	.	.	.	T	T	.	0.48	*	*	F	3.40	1.72
Asp	75	.	.	.	.	T	T	.	0.48	.	*	F	2.76	1.80
Ser	76	.	.	.	.	.	T	C	-0.11	.	*	F	2.07	0.76
Ser	77	.	.	B	.	.	.	.	0.49	*	*	F	0.73	0.50
Phe	78	.	.	B	.	.	.	.	0.03	*	*	.	0.24	0.46
Leu	79	.	.	B	.	.	.	.	-0.46	.	.	.	-0.40	0.34
Ala	80	.	.	B	.	.	T	.	-0.77	.	.	.	-0.20	0.22
Pro	81	.	.	B	.	.	T	.	-1.28	.	.	.	-0.20	0.37
Gly	82	.	.	.	.	T	T	.	-0.98	.	.	.	0.20	0.37
Phe	83	.	.	B	.	.	T	.	-0.28	.	.	.	-0.20	0.63
Thr	84	.	.	B	B	.	.	.	-0.32	.	.	.	-0.60	0.65
Leu	85	.	.	B	B	.	.	.	-0.08	*	*	.	-0.60	0.49
Gln	86	.	.	B	B	.	.	.	0.24	*	.	.	-0.29	0.56
Asn	87	.	.	B	.	.	T	.	0.63	*	.	F	0.87	0.76

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Val	88	.	.	B	.	.	T	.	1.03	*	*	F	1.93	1.84
Gly	89	.	.	.	.	.	T	C	1.00	*	.	F	2.74	1.42
Arg	90	.	.	.	.	T	T		1.51	*	.	F	3.10	0.87
Lys	91	.	.	.	.	.	T	C	1.51	*	.	F	2.74	1.58
Ser	92	.	.	.	.	.	T	C	1.20	*	.	F	2.43	2.76
Gly	93	.	.	.	.	.	T	C	1.84	.	.	F	2.38	2.04
Ser	94	.	.	.	.	.	T	C	1.38	.	.	F	2.33	1.57
Glu	95	.	.	.	.	.	.	C	1.06	.	.	F	1.63	0.97
Thr	96	.	.	.	.	.	.	C	1,01	.	.	F	2.04	1.51
Pro	97	.	.	.	.	.	.	C	1.00	.	.	F	2.60	1.96
Leu	98	.	.	.	.	.	.	C	1.34	.	.	F	2.04	1.63
Pro	99	A	.	.	.	.	.	.	0.83	.	.	F	1.58	1.89
Glu	100	A	A	.	.	.	.	.	0.24	.	.	F	1.12	1.01
Thr	101	A	A	.	.	.	.	.	0.52	.	.	F	0.86	1.23
Asp	102	A	A	.	.	.	.	.	0.07	.	.	F	0.60	1.08
Leu	103	A	A	.	.	.	.	.	0.18	.	.	.	0.30	0.34
Ala	104	A	A	.	.	.	.	.	0.14	.	.	.	-0.60	0.20
His	105	.	A	B	.	.	.	.	-0.16	*	.	.	-0.60	0.19
Cys	106	.	A	B	.	.	.	.	-0.19	*	.	.	-0.60	0.31
Phe	107	.	A	B	.	.	.	.	-0.50	*	.	.	-0.60	0.30
Tyr	108	.	.	B	.	.	T	.	-0.54	.	.	.	-0.20	0.32
Ser	109	.	.	.	.	T	T	.	0.04	.	*	F	0.35	0.44

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	110	.	.	.	.	T	T	.	-0.27	.	*	F	0.35	0.82
Thr	111	.	.	.	.	T	T	.	0.40	.	*	F	0.59	0.52
Val	112	.	.	B	B	.	.	.	0.89	.	*	F	0.93	0.65
Asn	113	.	.	.	B	T	.	.	0.83	.	*	F	1.72	1.01
Gly	114	.	.	.	B	.	.	C	0.83	.	*	F	1.61	0.94
Asp	115	.	.	.	.	.	T	C	0.59	.	*	F	2.40	1.69
Pro	116	.	.	.	.	.	T	C	0.31	.	*	F	2.16	1.06
Ser	117	.	.	.	.	.	T	C	0.58	.	*	F	1.92	1.08
Ser	118	A	.	.	.	.	T	.	-0.23	.	.	F	1.33	0.66
Ala	119	A	A	.	.	.	.	.	-0.19	.	.	.	-0.06	0.35
Ala	120	A	A	.	.	.	.	.	-1.00	.	.	.	-0.30	0.35
Ala	121	A	A	.	.	.	.	.	-1.46	.	.	.	-0.60	0.22
Leu	122	A	A	.	.	.	.	.	-1.16	.	.	.	-0.60	0.11
Ser	123	A	A	.	.	.	.	.	-1.20	.	.	.	-0.30	0.20
Leu	124	A	A	.	.	.	.	.	-1.47	*	*	.	-0.30	0.19
Cys	125	.	A	B	.	.	.	.	-0.77	*	*	.	-0.30	0.17
Glu	126	.	A	B	.	.	.	.	-0.52	*	*	.	0.30	0.25
Gly	127	A	.	.	.	.	.	.	-0.30	*	*	F	0.65	0.30
Val	128	A	.	.	.	.	.	.	-0.70	*	*	F	0.65	0.57
Arg	129	.	.	B	.	.	.	.	-0.13	*	*	F	0.65	0.29
Gly	130	.	.	B	B	.	.	.	-0.28	*	*	.	-0.60	0.45
Ala	131	.	.	B	B	.	.	.	-1.09	*	*	.	-0.60	0.50

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Phe	132	.	.	B	B	.	.	.	-1.09	*	*	.	-0.60	0.21
Tyr	133	.	.	B	B	.	.	.	-0.23	*	*	.	-0.60	0.21
Leu	134	.	A	B	B	.	.	.	-0.93	*	*	.	-0.60	0.36
Leu	135	.	A	B	B	.	.	.	-0.83	.	*	.	-0.60	0.42
Gly	136	A	A	.	B	.	.	.	-0.94	.	.	.	-0.60	0.42
Glu	137	A	A	.	.	.	.	.	-1.13	.	.	.	-0.60	0.44
Ala	138	A	A	.	B	.	.	.	-0.89	.	.	.	-0.60	0.38
Tyr	139	.	.	B	B	.	.	.	-0.29	.	.	.	-0.60	0.66
Phe	140	.	.	B	B	.	.	.	-0.29	.	.	.	-0.60	0.59
Ile	141	.	.	B	B	.	.	.	-0.16	.	.	.	-0.60	0.48
Gln	142	.	.	B	B	.	.	.	-0.74	.	.	.	-0.60	0.48
Pro	143	.	.	B	B	.	.	.	-0.74	.	.	.	-0.60	0.55
Leu	144	.	A	.	.	.	.	C	-0.80	*	.	.	-0.40	0.80
Pro	145	.	A	.	.	.	.	C	-0.10	*	.	.	-0.10	0.62
Ala	146	A	A	.	.	.	.	.	0.90	*	*	.	0.30	0.69
Ala	147	A	A	.	.	.	.	.	0.09	*	.	.	0.75	1.64
Ser	148	A	A	.	.	.	.	.	-0.29	*	.	F	0.75	0.88
Glu	149	A	A	.	.	.	.	.	0.21	*	.	F	0.45	0.88
Arg	150	A	A	.	.	.	.	.	-0.17	*	.	F	0.60	1.25
Leu	151	A	A	.	.	.	.	.	-0.17	*	.	.	0.30	0.94
Ala	152	A	A	.	.	.	.	.	0.21	*	*	.	0.30	0.55
Thr	153	A	A	.	.	.	.	.	0.17	*	*	.	0.04	0.43

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ala	154	A	A	.	.	.	.	.	0.17	.	.	.	0.08	0.52
Ala	155	.	.	.	.		T	C	0.10	.	*	F	2.07	0.89
Pro	156	.	.	.	.	.	T	C	0.70	.	.	F	2.86	1.24
Gly	157	.	.	.	.	T	T	.	1.08	.	.	F	3.40	1.90
Glu	158	.	.	.	.	.	T	C	0.80	.	.	F	2.86	2.90
Lys	159	.	.	.	.	.	.	C	1.18	.	.	F	2.32	1.90
Pro	160	.	.	.	.	.	.	C	0.96	.	*	F	1.98	2.97
Pro	161	.	.	.	.	.	.	C	1.17	.	*	F	1.64	1.41
Ala	162	A	A	.	.	.	.	.	0.81	.	*	F	0.60	1.22
Pro	163	A	A	.	.	.	.	.	0.78	.	*	.	-0.60	0.68
Leu	164	A	A	.	.	.	.	.	-0.08	.	*	.	-0.60	0.60
Gln	165	A	A	.	.	.	.	.	-0.68	*	*	.	-0.60	0.49
Phe	166	.	A	B	.	.	.	.	-0.36	*	*	.	-0.60	0.26
His	167	.	A	B	.	.	.	.	0.34	*	*	.	-0.26	0.62
Leu	168	.	A	B	.	.	.	.	0.56	*	*	.	0.38	0.70
Leu	169	.	A	B	.	.	.	.	1.48	*	*	.	0.87	1.31
Arg	170	.	.	.	.	T	T	.	1.48	*	.	F	3.06	1.88
Arg	171	.	.	.	.	T	T	.	1.83	*	.	F	3.40	3.96
Asn	172	.	.	.	.	T	T	.	1.87	*	.	F	3.06	4.75
Arg	173	.	.	.		T	T	.	1.82	*	.	F	2.72	4.05
Gln	174	.	.	.	.	T	.	.	2.29	.	.	F	2.43	1.53
Gly	175	.	.	.	.	T	.	.	1.83	.	.	F	2.19	0.94

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asp	176	.	.	.	.	T	T	.	1.41	.	*	F	2.30	0.48
Val	177	.	.	B	.	.	T		0.74	*	.	F	1.85	0.40
Gly	178	.	.	.	.	T	T	.	0.29	*	.	F	2.50	0.22
Gly	179	.	.	B	.	.	T	.	-0.57	.	*	F	1.85	0.13
Thr	180	.	.	B	B	.	.	.	-1.08	.	*	F	0.30	0.13
Cys	181	.	.	B	B	.	.	.	-1.08	.	.	.	-0.10	0.10
Gly	182	.	.	B	B	.	.	.	-0.22	.	.	.	-0.05	0.16
Val	183	.	.	B	B	.	.	.	0.12	.	.	.	0.30	0.19
Val	184	.	.	B	B	.	.	.	0.26	*	*	.	0.90	0.60
Asp	185	.	.	B	.	.	T	.	0.68	*	*	F	1.75	0.94
Asp	186	.	.	B	.	.	T	.	1.13	*	*	F	2.20	2.49
Glu	187	.	.	B	.	.	T	.	1.17	*	*	F	2.50	5.18
Pro	188	.	.	.	.	.	T	C	1.68	*	*	F	3.00	4.48
Arg	189	.	.	.	.	.	T	C	2.58	*	*	F	2.70	2.66
Pro	190	.	.	.	.	.	T	C	1.99	*	*	F	2.40	3.07
Thr	191	.	.	.	.	.	T	C	1.99	*	*	F	2.10	2.00
Gly	192	.	.	.	.	.	T	C	1.68	*	*	F	1.80	1.77
Lys	193	A	A	.	.	.	.	.	1.89	*	*	F	0.90	1.65
Ala	194	A	A	.	.	.	.	.	1.78	*	*	F	0.90	1.98
Glu	195	A	A	.	.	.	.	.	1.99	.	*	F	0.90	3.35
Thr	196	A	A	.	.	.	.	.	2.30	.	*	F	0.90	2.90
Glu	197	A	A	.	.	.	.	.	2.64	.	*	F	0.90	4.79

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asp	198	A	A	.	.	.	.	.	2.26	.	*	F	0.90	4.79
Glu	199	A	A	.	.	.	.	.	2.53	.	.	F	0.90	3.29
Asp	200	A	.	.	.	.	T	.	2.53	.	.	F	1.30	2.74
Glu	201	A	.	.	.	.	T	.	2.50	.	.	F	1.30	2.84
Gly	202	A	.	.	.	.	T	.	2.50	.	.	F	1.30	1.62
Thr	203	A	.	.	.	.	T	.	2.50	.	.	F	1.30	1.68
Glu	204	A	A	.	.	.	.	.	2.50	*	.	F	0.90	1.62
Gly	205	A	A	.	.	.	.	.	2.16	*	.	F	1.20	2.84
Glu	206	A	A	.	.	.	.	.	1.94	*	.	F	1.50	1.95
Asp	207	.	A	.	.	T	.	.	2.29	*	.	F	2.20	1.74
Glu	208	.	A	.	.	.	.	C	2.31	*	.	F	2.30	3.04
Gly	209	.	.	.	.	.	T	C	2.01	*	.	F	3.00	1.85
Pro	210	.	.	.	.	T	T	.	2.14	.	.	F	2.60	1.48
Gln	211	.	.	.	.	T	T	.	2.14	.	.	F	2.30	1.32
Trp	212	.	.	.	.	.	T	C	2.14	.	.	F	1.44	2.32
Ser	213	.	.	.	.	.	.	C	1.93	.	.	F	1.78	2.50
Pro	214	.	.	.	.	T	T	.	1.69	.	.	F	2.12	2.23
Gln	215	.	.	.	.	.	T	C	1.09	.	.	F	1.56	2.15
Asp	216	.	.	.	.	.	T	C	1.09	.	*	F	2.40	1.32
Pro	217	.	.	.	.	.	T	C	1.03	.	.	F	2.16	1.48
Ala	218	.	.	.	.	T	.	.	0.48	.	.	F	1.77	0.85
Leu	219	.	.	B	.	.	.	.	0.34	*	.	F	0.53	0.38

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gln	220	.	.	B	.	.	.	.	0.34	*	.	F	-0.01	0.24
Gly	221	.	.	B	.	.	T	.	0.13	*	*	F	-0.05	0.41
Val	222	.	.	B	.	.	T	.	0.03	*	.	F	-0.05	0.77
Gly	223	.	.	B	.	.	T	.	0.28	*	.	F	0.25	0.64
Gln	224	.	.	B	.	.	T	.	0.78	*	*	F	0.25	0.64
Pro	225	.	.	B	.	.	.	.	0.43	.	.	F	0.20	1.25
Thr	226	.	.	.	.	T	.	.	0.48	.	*	F	0.60	1.25
Gly	227	.	.	.	.	.	T	C	0.44	*	*	F	0.45	0.97
Thr	228	.	.	B	.	.	T	.	0.90	*	*	F	0.25	0.44
Gly	229	.	.	B	.	.	T	.	0.94	.	*	F	0.85	0.60
Ser	230	.	.	B	.	.	T	.	1.20	.	*	F	1.30	1.20
Ile	231	.	A	B	.	.	.	.	1.62	.	*	F	0.90	1.67
Arg	232	.	A	B	.	.	.	.	1.27	.	*	F	0.90	3.30
Lys	233	.	A	B	.	.	.	.	0.72	.	.	F	0.90	2.13
Lys	234	.	A	B	B	.	.	.	0.77	.	.	F	0.90	2.26
Arg	235	.	A	B	B	.	.	.	0.77	.	.	F	0.90	1.55
Phe	236	.	.	B	B	.	.	.	1.62	.	*	.	0.75	1.04
Val	237	.	.	B	B	.	.	.	1.62	.	*	.	0.30	0.71
Ser	238	.	.	B	.	.	T	.	1.33	*	*	.	0.70	0.71
Ser	239	.	.	.	.	.	T	C	0.43	*	.	.	0.15	1.28
His	240	.	.	.	.	.	T	C	0.32	*	*	.	0.45	1.28
Arg	241	.	.	.	.	.	T	C	0.71	*	.	.	1.05	1.65

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Tyr	242	A	.	.	B	.	.	.	0.97	*	.	.	0.45	1.78
Val	243	A	.	.	B	.	.	.	0.46	*	.	.	0.45	1.29
Glu	244	.	.	B	B	.	.	.	-0.10	*	.	.	-0.30	0.54
Thr	245	.	.	B	B	.	.	.	-0.66	*	.	.	-0.60	0.26
Met	246	A	.	B	B	.	.	.	-0.77	*	.	.	-0.60	0.35
Leu	247	A	.	.	B	.	.	.	-0.52	.	.	.	0.30	0.34
Val	248	A	.	.	B	.	.	.	0.03	.	.	.	-0.30	0.41
Ala	249	A	.	.	B	.	.	.	-0.57	.	.	.	-0.30	0.55
Asp	250	A	.	.	.	.	T	.	-0.84	.	.	F	0.25	0.66
Gln	251	A	.	.	.	.	T	.	-0.24	.	.	F	0.25	0.90
Ser	252	A	.	.	.	.	T	.	-0.13	.	.	F	1.30	1.54
Met	253	A	.	.	.	.	T	.	0.69	.	*	.	0.70	0.80
Ala	254	A	.	.	.	.	.	.	0.93	.	*	.	-0.10	0.63
Glu	255	A	.	.	.	.	.	.	0.63	.	*	.	-0.10	0.46
Phe	256	A	.	.	.	.	.	.	0.29	.	*	.	-0.10	0.63
His	257	A	.	.	.	.	T	.	-0.22	*	.	.	0.10	0.61
Gly	258	A	.	.	.	.	T	.	0.42	*	.	F	0.25	0.29
Ser	259	A	.	.	.	.	T	.	0.98	*	*	F	0.25	0.68
Gly	260	A	.	.	.	.	T	.	0.73	*	*	F	0.85	0.68
Leu	261	A	A	.	.	.	.	.	0.62	.	.	F	0.00	1.07
Lys	262	A	A	.	.	.	.	.	-0.16	.	.	.	-0.60	0.66
His	263	.	A	B	.	.	.	.	-0.12	*	.	.	-0.60	0.55

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Tyr	264	.	A	B	.	.	.	.	-0.63	*	.	.	-0.60	0.96
Leu	265	.	A	B	.	.	.	.	-0.99	*	.	.	-0.60	0.40
Leu	266	.	A	B	.	.	.	.	-0.48	*	.	.	-0.60	0.25
Thr	267	.	A	B	.	.	.	.	-1.38	*	.	.	-0.60	0.22
Leu	268	.	A	B	.	.	.	.	-1.93	*	.	.	-0.60	0.19
Phe	269	A	A	.	.	.	.	.	-2.28	*	*	.	-0.60	0.24
Ser	270	A	A	.	.	.	.	.	-1.36	*	*	.	-0.60	0.17
Val	271	A	A	.	.	.	.	.	-1.36	*	*	.	-0.60	0.39
Ala	272	A	A	.	.	.	.	.	-1.29	*	*	.	-0.60	0.38
Ala	273	A	A	.	.	.	.	.	-0.43	*	*	.	-0.60	0.44
Arg	274	A	A	.	.	.	.	.	0.23	*	*	.	-0.15	1.18
Leu	275	A	A	.	.	.	.	.	0.32	*	*	.	0.45	1.59
Tyr	276	.	.	.	.	T	.	.	0.88	*	*	.	1.39	2.44
Lys	277	.	.	B	.	.	.	.	0.58	*	*	F	1.48	1.67
His	278	.	.	B	.	.	T	.	1.28	.	*	F	1.12	1.42
Pro	279	.	.	B	.	.	T	.	1.17	.	*	F	2.36	1.77
Ser	280	.	.	.	.	T	T	.	1.68	.	*	F	3.40	1.43
Ile	281	.	.	B	.	.	T	.	1.07	.	*	F	2.36	1.41
Arg	282	.	.	B	B	.	.	.	0.72	.	*	F	1.47	0.67
Asn	283	.	.	B	B	.	.	.	-0.06	*	*	F	1.13	0.67
Ser	284	.	.	B	B	.	.	.	-0.70	*	*	F	0.19	0.79
Val	285	.	.	B	B	.	.	.	-1.26	*	*	.	-0.30	0.30

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ser	286	.	.	B	B	.	.	.	-1.22	.	*	.	-0.60	0.14
Leu	287	.	.	B	B	.	.	.	-1.29	.	*	.	-0.60	0.08
Val	288	.	.	B	B	.	.	.	-2.18	*	.	.	-0.60	0.21
Val	289	.	.	B	B	.	.	.	-2.69	.	*	.	-0.60	0.11
Val	290	.	.	B	B	.	.	.	-2.69	.	.	.	-0.60	0.11
Lys	291	.	.	B	B	.	.	.	-3.28	.	.	.	-0.60	0.11
Ile	292	.	.	B	B	.	.	.	-2.50	.	.	.	-0.60	0.10
Leu	293	.	.	B	B	.	.	.	-1.64	.	*	.	-0.60	0.19
Val	294	.	.	B	B	.	.	.	-0.79	.	.	.	-0.30	0.16
Ile	295	.	.	B	B	.	.	.	0.07	.	*	.	0.00	0.39
His	296	A	.	.	B	.	.	.	0.07	.	*	.	0.90	0.81
Asp	297	A	.	.	B	.	.	.	0.61	.	.	F	1.80	2.19
Glu	298	A	.	.	.	.	.	.	1.21	*	.	F	2.30	3.09
Gln	299	.	.	.	.	T	.	.	2.07	*	.	F	3.00	3.51
Lys	300	.	.	.	.	.	.	C	2.10	.	.	F	2.50	3.64
Gly	301	.	.	.	.	.	T	C	1.82	.	.	F	2.40	1.56
Pro	302	.	.	.	.	.	T	C	1.52	.	.	F	2.10	1.30
Glu	303	.	.	B	.	.	T	.	1.52	*	.	F	1.45	0.87
Val	304	A	.	.	.	.	T	.	0.93	*	.	F	1.00	1.42
Thr	305	A	.	.	.	.	T	.	0.30	.	*	F	0.85	0.93
Ser	306	A	.	.	.	.	T	.	-0.17	.	*	F	0.85	0.54
Asn	307	A	.	.	.	.	T	.	-0.27	.	*	F	-0.05	0.60

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ala	308	A	.	.	.	.	T	.	-1.08	*	*	.	-0.20	0.60
Ala	309	A	.	.	.	.	.	.	-0.11	*	*	.	-0.40	0.37
Leu	310	A	.	.	.	.	.	.	0.20	*	*	.	-0.10	0.45
Thr	311	.	.	B	.	.	.	.	-0.20	*	*	.	-0.10	0.72
Leu	312	.	.	B	.	.	.	.	-0.87	*	*	.	-0.40	0.61
Arg	313	.	.	B	.	.	.	.	-0.28	*	*	.	-0.40	0.40
Asn	314	.	.	.	.	T	.	.	0.02	*	*	.	0.30	0.44
Phe	315	.	.	.	.	T	T	.	0.83	*	*	.	0.20	0.57
Cys	316	.	.	.	.	T	T	.	1.19	*	*	.	0.20	0.50
Asn	317	.	.	.	.	T	T	.	2.00	*	*	.	0.20	0.62
Trp	318	.	.	.	.	T	T	.	1.86	*	.	.	0.35	1.25
Gln	319	.	.	.	.	T	.	.	1.86	.	.	.	0.45	3.16
Lys	320	.	.	.	.	T	.	.	2.34	*	.	F	0.60	3.16
Gln	321	.	.	.	.	T	.	.	2.80	.	.	F	0.94	4.65
His	322	.	.	.	.	.	.	C	2.50	*	.	F	1.68	4.15
Asn	323	.	.	.	.	.	.	C	2.79	*	.	F	2.02	2.78
Pro	324	.	.	.	.	.	T	C	2.90	.	.	F	2.56	2.68
Pro	325	.	.	.	.	T	T	.	2.86	*	.	F	3.40	3.86
Ser	326	.	.	.	.	.	T	C	2.27	.	.	F	2.86	4.01
Asp	327	.	.	.	.	.	T	C	2.30	.	.	F	2.52	2.62
Arg	328	A	A	.	.	.	.	.	2.27	.	.	F	1.58	2.94
Asp	329	A	A	.	.	.	.	.	2.23	*	.	F	1.24	2.98

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ala	330	A	A	.	.	.	.	.	2.44	*	.	.	0.90	2.80
Glu	331	A	A	.	.	.	.	.	2.43	*	.	.	0.75	2.38
His	332	A	.	.	.	.	T	.	1.84	*	.	.	1.15	2.06
Tyr	333	A	.	.	.	.	T	.	0.84	*	.	.	0.85	2.06
Asp	334	A	.	.	.	.	T	.	0.03	.	.	.	0.70	0.83
Thr	335	A	.	.	.	.	T	.	-0.08	.	.	.	-0.20	0.51
Ala	336	A	A	.	.	.	.	.	-0.39	*	.	.	-0.60	0.28
Ile	337	A	A	.	.	.	.	.	-0.24	*	.	.	-0.60	0.24
Leu	338	.	A	B	.	.	.	.	0.00	.	.	.	-0.60	0.33
Phe	339	.	A	B	.	.	.	.	0.00	.	*	.	-0.60	0.56
Thr	340	.	A	B	.	.	.	.	-0.50	.	.	F	0.00	1.34
Arg	341	.	A	B	.	.	.	.	-0.58	.	*	F	0.25	1.34
Gln	342	.	A	.	.	T	.	.	-0.03.	.	*	F	1.35	0.83
Asp	343	.	A	.	.	T	.	.	0.48	.	*	F	1.60	0.57
Leu	344	.	A	.	.	T	.	.	1.18	*	.	F	2.15	0.39
Cys	345	.	.	.	.	T	T	.	1.18	.	*	F	2.50	0.39
Gly	346	.	.	.	.	T	T	.	0.40	.	*	F	2.25	0.34
Ser	347	.	.	.	.	T	T	.	0.40	.	.	F	1.10	0.22
Gln	348	.	.	B	.	.	T	.	0.09	.	.	F	1.35	0.68
Thr	349	.	.	B	.	.	.	.	0.09	.	.	F	0.90	0.99
Cys	350	.	.	B	.	.	.	.	0.41	.	.	F	0.05	0.61
Asp	351	.	.	B	.	.	T	.	0.16	*	.	F	0.25	0.35

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Thr	352	.	.	B	.	.	T	.	-0.13	.	.	F	0.25	0.24
Leu	353	.	.	B	.	.	T	.	-0.13	.	.	.	0.10	0.45
Gly	354	.	.	B	.	.	T	.	-0.68	.	.	.	0.70	0.45
Met	355	.	.	B	.	.	.	.	-0.36	.	.	.	-0.10	0.23
Ala	356	.	.	B	.	.	.	.	-0.67	.	.	.	-0.10	0.28
Asp	357	.	.	B	.	.	T	.	-1.21	.	.	.	0.10	0.41
Val	358	.	.	B	.	.	T	.	-1.07	.	.	.	0.10	0.30
Gly	359	.	.	B	.	.	T	.	-0.72	.	.	.	0.10	0.16
Thr	360	.	.	B	.	.	T	.	-0.33	.	.	.	0.70	0.16
Val	361	.	.	B	.	.	.	.	-0.04	.	*	.	0.24	0.34
Cys	362	.	.	B	.	.	.	.	0.07	*	.	.	1.18	0.46
Asp	363	.	.	B	.	.	T	.	0.62	*	.	F	1.87	0.62
Pro	364	.	.	.	.	T	T	.	0.30	*	.	F	3.06	1.12
Ser	365	.	.	.	.	T	T	.	0.31	*	.	F	3.40	1.12
Arg	366	.	.	.	.	T	T	.	0.31	*	.	F	2.91	0.90
Ser	367	.	.	.	B	T	.	.	0.09	*	.	F	1.87	0.43
Cys	368	.	.	B	B	.	.	.	0.09	*	.	.	0.38	0.22
Ser	369	.	.	B	B	.	.	.	0.30	*	.	.	0.64	0.20
Val	370	.	.	B	B	.	.	.	0.60	*	.	.	0.30	0.25
Ile	371	.	.	B	B	.	.	.	0.14	*	.	.	0.60	0.77
Glu	372	.	.	B	B	.	.	.	-0.37	.	.	.	0.60	0.57
Asp	373	A	.	.	.	.	T	.	0.30	.	.	F	1.15	0.63

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asp	374	A	.	.	.	.	T	.	0.01	*	.	.	1.30	1.56
Gly	375	A	.	.	.	.	T	.	0.28	.	.	.	1.00	0.91
Leu	376	A	.	.	.	.	T	.	0.47	*	.	.	0.70	0.55
Gln	377	A	A	.	.	.	.	.	0.16	.	.	.	-0.30	0.29
Ala	378	A	A	.	.	.	.	.	-0.16	*	.	.	-0.60	0.42
Ala	379	A	A	.	.	.	.	.	-0.74	*	.	.	-0.60	0.73
Phe	380	A	A	.	.	.	.	.	-0.43	*	.	.	-0.60	0.43
Thr	381	A	A	.	.	.	.	.	0.38	*	*	.	-0.60	0.57
Thr	382	A	A	.	.	.	.	.	-0.43	*	.	.	-0.30	0.98
Ala	383	A	A	.	.	.	.	.	-0.19	*	.	.	-0.60	0.94
His	384	A	A	.	.	.	.	.	0.37	*	.	.	-0.30	0.64
Glu	385	A	A	.	.	.	.	.	0.21	*	.	.	-0.30	0.61
Leu	386	A	A	.	.	.	.	.	-0.18	*	.	.	-0.30	0.45
Gly	387	A	.	.	B	.	.	.	0.13	*	.	.	-0.60	0.28
His	388	A	.	.	B	.	.	.	0.12	*	.	.	-0.60	0.26
Val	389	A	.	.	B	.	.	.	-0.06	*	.	.	-0.60	0.32
Phe	390	A	.	.	B	.	.	.	-0.09	*	.	.	-0.60	0.49
Asn	391	.	.	B	B	.	.	.	0.72	*	.	.	-0.60	0.49
Met	392	.	.	B	.	.	T	.	1.07	*	.	.	0.25	1.11
Pro	393	A	.	.	.	.	T	.	0.51	*	.	.	0.85	2.14
His	394	.	.	.	.	T	T	.	1.41	*	.	F	1.70	1.34
Asp	395	A	.	.	.	.	T	.	2.11	*	.	F	1.30	2.72

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asp	396	A	A	.	.	.	.	.	1.44	*	.	F	0.90	3.04
Ala	397	A	A	.	.	.	.	.	1.46	*	.	F	0.90	1.20
Lys	398	A	A	.	.	.	.	.	1.37	*	*	F	0.75	0.73
Gln	399	A	A	.	.	.	.	.	0.59	.	*	.	0.60	0.58
Cys	400	.	A	B	.	.	.	.	0.59	.	*	.	-0.30	0.48
Ala	401	.	A	B	.	.	.	.	0.24	.	*	.	0.30	0.38
Ser	402	.	.	B	.	.	T	.	-0.02	.	*	.	0.10	0.22
Leu	403	.	.	B	.	.	T	.	-0.07	.	.	.	0.04	0.30
Asn	404	.	.	.	.	T	T	.	-0.07	.	.	.	0.68	0.48
Gly	405	.	.	.	.	T	T	.	0.60	.	.	F	1.37	0.62
Val	406	.	.	.	.	.	.	C	0.89	.	.	F	1.96	1.26
Asn	407	.	.	.	.	.	T	C	1.16	.	.	F	2.40	1.05
Gln	408	A	.	.	.	.	T	.	1.37	*	.	F	1.96	1.44
Asp	409	A	.	.	.	.	T	.	0.77	*	.	F	1.72	1.92
Ser	410	A	.	.	.	.	T	.	0.52	.	.	.	1.33	1.18
His	411	A	A	.	.	.	.	.	1.08	.	*	.	-0.06	0.69
Met	412	A	A	.	.	.	.	.	0.48	.	.	.	0.30	0.55
Met	413	A	A	.	.	.	.	.	-0.33	.	.	.	-0.60	0.41
Ala	414	A	A	.	.	.	.	.	-0.63	.	.	.	-0.60	0.25
Ser	415	A	A	.	.	.	.	.	-0.33	*	.	.	-0.60	0.34
Met	416	A	A	.	.	.	.	.	-1.11	*	*	.	-0.60	0.55
Leu	417	A	.	.	.	.	T	.	-0.51	*	.	.	-0.20	0.45

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ser	418	A	.	.	.	.	T	.	0.06	*	.	.	0.38	0.56
Asn	419	A	.	.	.	.	T	.	0.34	.	.	.	0.66	0.76
Leu	420	.	.	.	.	.	T	C	0.64	.	.	.	1.29	1.24
Asp	421	.	.	.	.	T	T	.	1.03	.	.	.	2.37	1.60
His	422	.	.	.	.	T	T	.	1.56	.	.	F	2.80	1.54
Ser	423	.	.	.	.	.	T	C	1.56	.	.	F	1.72	1.97
Gln	424	.	.	.	.	.	T	C	1.34	.	.	F	1.44	1.58
Pro	425	.	.	.	.	T	.	.	1.49	.	.	F	0.86	1.79
Trp	426	.	.	.	.	T	.	.	1.19	.	.	F	0.43	0.72
Ser	427	.	.	.	.	.	T	C	0.63	.	.	F	0.15	0.55
Pro	428	.	.	.	.	T	T	.	0.69	.	.	F	0.35	0.36
Cys	429	.	.	.	.	T	T	.	0.09	.	.	.	0.20	0.54
Ser	430	.	.	B	.	.	T	.	-0.59	.	.	.	-0.20	0.40
Ala	431	.	.	B	B	.	.	.	-0.61	.	.	.	-0.60	0.18
Tyr	432	.	.	B	B	.	.	.	-0.61	.	.	.	-0.60	0.49
Met	433	.	.	B	B	.	.	.	-1.10	.	.	.	-0.60	0.49
Ile	434	.	.	B	B	.	.	.	-1.24	*	.	.	-0.60	0.42
Thr	435	.	.	B	B	.	.	.	-0.94	*	.	.	-0.60	0.22
Ser	436	.	.	B	B	.	.	.	-0.36	*	.	.	-0.60	0.37
Phe	437	.	.	B	B	.	.	.	-0.46	*	.	.	-0.60	0.85
Leu	438	.	.	B	.	.	T	.	0.11	*	.	F	0.56	0.58
Asp	439	.	.	.	.	T	T	.	0.66	*	.	F	1.27	0.59

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asn	440	.	.	.	.	.	T	C	0.97	.	.	F	1.38	0.68
Gly	441	.	.	.	.	T	T	.	0.60	.	.	F	2.94	1.42
His	442	.	.	.	.	T	T	.	0.49	.	.	F	3.10	0.46
Gly	443	A	.	.	.	.	T	.	0.70	.	.	F	1.49	0.23
Glu	444	A	.	.	.	.	T	.	0.70	.	.	.	1.03	0.23
Cys	445	.	.	B	.	.	T	.	0.74	.	*	.	1.32	0.29
Leu	446	.	A	B	.	.	.	.	0.88	.	.	.	1.25	0.58
Met	447	.	A	B	.	.	.	.	0.91	*	.	.	1.28	0.52
Asp	448	.	A	.	.	T	.	.	1.26	*	.	F	2.02	1.67
Lys	449	.	A	.	.	.	.	C	1.04	*	.	F	2.16	3.26
Pro	450	.	.	.	.	T	T	.	0.82	*	*	F	3.40	5.10
Gln	451	.	.	.	.	T	T	.	1.63	*	*	F	3.06	2.14
Asn	452	.	.	B	.	.	T	.	1.42	*	*	F	2.02	1.85
Pro	453	.	.	B	.	.	T	.	1.21	*	*	F	0.63	0.99
Ile	454	.	.	B	.	.	.	.	0.82	*	*	F	0.09	0.88
Gln	455	.	.	B	.	.	.	.	1.03	*	*	F	-0.25	0.54
Leu	456	.	.	B	.	.	T	.	0.22	*	*	F	0.25	0.59
Pro	457	.	.	B	.	.	T	.	0.01	*	*	F	0.25	0.69
Gly	458	.	.	B	.	.	T	.	-0.12	.	*	F	0.25	0.62
Asp	459	.	.	B	.	.	T	.	0.46	.	*	F	0.25	0.74
Leu	460	.	.	.	.	.	T	C	0.16	.	*	F	1.05	0.69
Pro	461	.	.	B	.	.	T	.	0.72	.	*	F	0.85	0.93

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	462	.	.	B	.	.	T	.	0.93	.	.	F	0.25	0.88
Thr	463	.	.	B	.	.	T	.	0.69	.	*	F	0.74	1.78
Ser	464	.	.	B	.	.	.	.	0.69	*	.	F	1.48	1.16
Tyr	465	.	.	.	.	T	.	.	1.61	*	.	F	2.22	1.88
Asp	466	.	.	.	.	T	T	.	1.82	.	.	.	2.61	2.56
Ala	467	.	.	.	.	T	T	.	1.50	*	.	F	3.40	3.31
Asn	468	.	.	.	.	T	T	.	1.81	.	*	F	2.76	1.13
Arg	469	.	.	B	.	.	T	.	1.41	.	*	F	2.32	1.17
Gln	470	.	.	B	B	.	.	.	1.34	*	*	.	0.53	1.01
Cys	471	.	.	B	B	.	.	.	0.64	*	*	.	0.04	0.90
Gln	472	.	.	B	B	.	.	.	0.89	.	.	.	-0.60	0.40
Phe	473	.	.	B	B	.	.	.	0.89	.	.	.	-0.26	0.23
Thr	474	.	.	B	B	.	.	.	0.78	.	.	.	0.08	0.74
Phe	475	.	.	.	B	T	.	.	0.48	.	*	.	1.72	0.71
Gly	476	.	.	.	.	T	T	.	1.19	.	*	F	2.76	1.10
Glu	477	.	.	.	.	T	T	.	1.16	.	*	F	3.40	1.52
Asp	478	.	.	.	.	T	T	.	1.19	*	.	F	3.06	2.39
Ser	479	.	.	.	.	T	T	.	1.29	*	.	F	2.72	1.30
Lys	480	.	.	.	.	T	.	.	1.99	*	.	F	2.43	1.16
His	481	.	.	.	.	T	.	.	1.74	*	.	F	2.34	1.16
Cys	482	.	.	.	.	.	T	C	1.16	*	.	F	2.10	0.87
Pro	483	A	.	.	.	.	T	.	0.86	.	.	F	2.15	0.44

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asp	484	.	.	.	.	T	T	.	0.84	*	.	F	2.50	0.43
Ala	485	A	.	.	.	.	T	.	0.13	*	.	F	2.00	1.17
Ala	486	A	.	.	.	.	.	.	-0.13	.	.	F	1.40	0.41
Ser	487	.	.	B	.	T	T	.	0.22	.	.	F	1.75	0.33
Thr	488	.	.	B	.	.	T	.	-0.38	*	.	F	0.50	0.46
Cys	489	.	.	B	.	.	T	.	-0.67	*	.	F	-0.05	0.38
Ser	490	.	.	B	.	.	T	.	-0.74	.	.	F	-0.05	0.30
Thr	491	.	.	B	B	.	.	.	-0.47	.	.	.	-0.60	0.11
Leu	492	.	.	B	B	.	.	.	-0.51	.	.	.	-0.60	0.30
Trp	493	.	.	B	B	.	.	.	-0.51	.	.	.	-0.60	0.22
Cys	494	.	.	B	B	.	.	.	-0.14	.	.	.	-0.60	0.22
Thr	495	.	.	B	B	T	.	.	-0.19	.	.	F	-0.05	0.36
Gly	496	.	.	.	B	T	.	.	-0.22	.	.	F	-0.05	0.34
Thr	497	.	.	.	.	T	T	.	-0.27	.	.	F	0.65	0.62
Ser	498	.	.	.	.	T	T	.	-0.79	.	.	F	0.65	0.32
Gly	499	.	.	.	.	T	T	.	-0.98	.	.	F	0.35	0.27
Gly	500	.	.	.	.	T	T	.	-1.33	.	.	F	0.35	0.14
Val	501	.	.	B	B	.	.	.	-0.99	.	.	.	-0.60	0.05
Leu	502	.	.	B	B	.	.	.	-0.99	.	.	.	-0.60	0.10
Val	503	.	.	B	B	.	.	.	-0.64	.	.	.	-0.60	0.14
Cys	504	.	.	B	.	.	T	.	-0.33	.	.	.	-0.20	0.38
Gln	505	.	.	B	.	.	T	.	-0.69	.	.	.	0.10	0.62

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Thr	506	.	.	B	.	.	T	.	-0.04	.	.	F	0.25	0.72
Lys	507	.	.	B	.	.	T	.	0.48	.	.	F	0.40	2.09
His	508	.	.	.	.	.	.	C	0.74	.	.	.	-0.05	1.27
Phe	509	.	.	B	.	.	.	.	1.41	.	.	.	-0.40	0.89
Pro	510	.	.	.	.	T	.	.	1.07	.	.	.	0.30	0.74
Trp	511	.	.	.	.	T	T	.	1.07	.	.	.	0.20	0.54
Ala	512	.	.	.	.	T	T	.	0.72	.	.	.	0.51	0.90
Asp	513	.	.	.	.	T	T	.	0.09	.	.	F	1.27	0.78
Gly	514	.	.	.	.	T	T	.	0.44	.	.	F	1.58	0.40
Thr	515	.	.	.	.	T	T	.	0.66	.	.	F	2.49	0.39
Ser	516	.	.	.	.	T	T	.	0.60	.	*	F	3.10	0.40
Cys	517	.	.	.	.	T	T	.	1.23	.	*	F	2.49	0.40
Gly	518	.	.	.	.	T	T	.	0.94	.	*	F	2.48	0.56
Glu	519	.	.	.	.	T	.	.	0.62	.	*	F	1.67	0.44
Gly	520	.	.	.	.	T	.	.	0.04	.	*	F	1.36	0.44
Lys	521	.	.	.	.	T	.	.	0.34	.	*	F	0.45	0.31
Trp	522	.	.	.	.	T	.	.	0.67	.	*	.	0.90	0.29
Cys	523	.	.	B	.	.	T	.	1.06	.	*	.	-0.20	0.29
Ile	524	.	.	B	.	.	T	.	0.39	.	*	.	0.70	0.29
Asn	525	.	.	.	.	T	T	.	-0.12	.	*	.	0.20	0.15
Gly	526	.	.	.	.	T	T	.	-0.17	*	*	F	0.65	0.20
Lys	527	.	.	.	.	T	.	.	0.17	*	*	F	0.45	0.47

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Cys	528	.	.	.	.	T	T	.	0.52	.	*	.	1.40	0.58
Val	529	.	.	B	.	.	T	.	1.41	*	*	.	1.04	0.85
Asn	530	.	.	B	.	.	T	.	1.52	*	.	F	1.83	0.71
Lys	531	.	.	B	.	.	T	.	1.91	*	.	F	2.32	2.58
Thr	532	.	.	B	.	.	T	.	1.83	*	.	F	2.66	6.96
Asp	533	.	.	.	.	T	T	.	1.80	*	.	F	3.40	5.89
Arg	534	.	.	.	.	T	T	.	2.66	*	.	F	3.06	2.55
Lys	535	.	.	B	.	.	T	.	2.34	*	.	F	2.32	2.95
His	536	.	.	B	.	.	.	.	2.09	*	.	F	1.78	2.55
Phe	537	.	.	B	.	.	.	.	1.70	*	.	F	1.44	2.01
Asp	538	.	.	B	.	.	.	.	1.67	*	.	F	0.65	0.87
Thr	539	.	.	B	.	.	.	.	1.21	*	.	F	-0.25	0.87
Pro	540	.	.	.	.	.	.	C	0.87	*	*	F	-0.05	1.00
Phe	541	.	.	.	.	T	.	.	0.61	.	*	F	0.45	0.80
His	542	.	.	.	.	T	T	.	0.97	.	*	.	0.20	0.58
Gly	543	.	.	.	.	T	T	.	0.37	.	*	.	0.20	0.37
Ser	544	.	.	.	.	T	T	.	0.39	.	*	.	0.20	0.43
Trp	545	.	.	.	.	T	T	.	0.26	.	*	.	0.20	0.33
Gly	546	.	.	.	.	.	.	C	0.74	.	*	.	-0.20	0.33
Met	547	.	.	.	.	T	.	.	0.49	.	.	.	0.00	0.38
Trp	548	.	.	.	.	T	.	.	0.49	.	.	.	0.00	0.38
Gly	549	.	.	.	.	.	T	C	0.79	.	.	.	0.00	0.38

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Pro	550	.	.	.	.	T	T	.	0.41	.	.	F	0.35	0.64
Trp	551	.	.	.	.	T	T	.	0.46	*	.	F	0.66	0.33
Gly	552	.	.	.	.	T	T	.	1.17	*	.	F	1.27	0.44
Asp	553	.	.	.	.	T	.	.	1.14	*	.	F	1.98	0.56
Cys	554	.	.	.	.	T	T	.	0.82	*	.	F	2.49	0.77
Ser	555	.	.	.	.	T	T	.	0.69	*	.	F	3.10	0.42
Arg	556	.	.	.	.	T	T	.	0.63	*	.	F	2.79	0.25
Thr	557	.	.	.	.	T	T	.	0.63	*	.	F	2.18	0.46
Cys	558	.	.	.	.	T	T	.	-0.22	*	.	F	1.87	0.34
Gly	559	.	.	.	.	T	T	.	0.44	*	.	F	1.56	0.13
Gly	560	.	.	.	.	T	T	.	0.50	*	.	F	0.65	0.15
Gly	561	.	.	.	.	T	T	.	0.08	*	*	F	0.35	0.45
Val	562	.	.	B	B	.	.	.	-0.21	*	*	.	-0.60	0.65
Gln	563	.	.	B	B	.	.	.	0.57	*	*	.	-0.60	0.65
Tyr	564	.	.	B	B	.	.	.	0.91	*	*	.	-0.15	1.29
Thr	565	.	.	B	B	.	.	.	0.59	*	*	.	0.79	3.01
Met	566	.	.	B	B	.	.	.	0.93	*	*	.	0.98	0.93
Arg	567	.	.	B	B	.	.	.	1.79	*	*	. .	1.62	0.99
Glu	568	.	.	.	.	T	.	.	1.58	*	*	F	2.86	1.11
Cys	569	.	.	.	.	T	T	.	0.97	*	.	F	3.40	1.73
Asp	570	.	.	.	.	T	T	.	1.07	*	..	F	2.91	0.66

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asn	571	.	.	.	.	.	T	C	1.71	*	.	F	2.37	0.59
Pro	572	.	.	.	.	.	T	C	1.60	*	.	F	2.52	2.18
Val	573	.	.	.	.	.	.	C	1.26	*	.	F	2.32	2.10
Pro	574	.	.	.	.	T	T	.	1.58	*	.	F	2.42	1.29
Lys	575	.	.	.	.	T	T	.	1.62	*	.	F	2.61	0.83
Asn	576	.	.	.	.	T	T	.	1.38	*	.	F	3.40	2.23
Gly	577	.	.	.	.	T	T	.	0.92	*	.	F	3.06	2.26
Gly	578	.	.	.	.	T	T	.	1.78	*	.	F	2.27	0.61
Lys	579	.	.	B	.	.	T	.	1.64	.	.	F	1.53	0.65
Tyr	580	.	.	B	.	.	T	.	1.64	.	.	F	1.19	0.65
Cys	581	.	.	B	.	.	T	.	1.76	.	.	F	1.30	1.32
Glu	582	.	.	B	.	.	.	.	1.24	.	*	F	1.10	1.29
Gly	583	.	.	B	B	.	.	.	1.70	.	*	F	0.75	0.61
Lys	584	.	.	B	B	.	.	.	1.41	.	*	F	0.90	2.24
Arg	585	.	.	B	B	.	.	.	1.77	.	*	F	1.15	2.02
Tyr	586	.	.	B	B	.	.	.	2.13	.	*	.	1.25	4.01
Arg	587	.	.	B	B	.	.	.	1.47	*	*	.	1.50	2.68
Tyr	588	.	.	B	.	.	T	.	1.81	*	*	.	2.00	0.73
Arg	589	.	.	.	.	T	T	.	0.96	*	*	.	2.50	1.59
Ser	590	.	.	.	.	T	T	.	0.84	*	*	.	2.10	0.67
Cys	591	.	.	.	.	T	T	.	1.70	.	*	.	1.85	0.74
Asn	592	.	A	.	.	T	.	.	0.92	.	*	.	1.50	0.63

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	593	.	A	B	.	.	.	.	0.96	.	.	.	0.89	0.25
Glu	594	.	A	B	.	.	.	.	0.84	.	.	F	1.13	0.73
Asp	595	.	A	.	.	T	.	.	1.17	.	.	F	2.17	0.76
Cys	596	.	.	B	.	.	T	.	1.81	.	.	F	2.66	1.48
Pro	597	.	.	.	.	T	T	.	1.47	*	*	F	3.40	1.37
Asp	598	.	.	.	.	T	T	.	2.32	*	*	F	2.91	0.81
Asn	599	.	.	.	.	T	T	.	2.01	*	.	F	3.02	3.03
Asn	600	.	.	.	.	T	T	.	1.31	*	.	F	2.98	2.83
Gly	601	.	.	.	.	T	T	.	2.09	*	.	F	2.94	1.47
Lys	602	.	.	.	.	.	T	C	2.30	*	*	F	2.70	1.79
Thr	603	.	.	.	.	.	T	C	2.30	*	.	F	3.00	1.92
Phe	604	A	A	.	.	.	.	.	2.30	*	.	F	2.10	3.37
Arg	605	A	A	.	.	.	.	.	1.63	.	.	F	1.80	2.91
Glu	606	A	A	.	.	.	.	.	1.98	*	.	F	1.50	1.08
Glu	607	A	A	.	.	.	.	.	1.34	*	.	F	1.20	2.17
Gln	608	A	A	.	.	.	.	.	1.62	*	.	F	0.90	1.12
Cys	609	A	A	.	.	.	.	.	2.32	*	*	.	0.60	0.88
Glu	610	A	A	.	.	.	.	.	2.21	.	*	.	0.60	0.81
Ala	611	A	A	.	.	.	.	.	1.51	.	*	.	0.60	0.81
His	612	A	A	.	.	.	.	.	1.21	*	.	.	0.45	1.32
Asn	613	A	A	.	.	.	.	.	1.26	*	*	.	0.45	1.02
Glu	614	A	A	.	.	.	.	.	1.33	*	.	.	0.45	2.02

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Phe	615	A	A	.	.	.	.	.	1.03	*	*	F	0.60	1.50
Ser	616	A	A	.	.	.	.	.	0.92	.	.	F	0.90	1.25
Lys	617	A	A	.	.	.	.	.	0.61	.	.	F	0.45	0.62
Ala	618	.	A	.	.	T	.	.	0.31	.	.	F	0.25	0.71
Ser	619	.	A	.	.	T	.	.	-0.03	.	.	F	0.85	0.71
Phe	620	.	.	.	.	T	.	.	0.46	.	.	F	1.26	0.35
Gly	621	.	.	.	.	T	T	.	0.17	.	.	F	1.07	0.54
Ser	622	.	.	.	.	.	T	C	-0.73	.	*	F	1.08	0.41
Gly	623	.	.	.	.	.	T	C	-0.14	.	.	F	0.99	0.35
Pro	624	.	.	.	.	.	T	C	-0.13	.	.	F	2.10	0.61
Ala	625	.	A	.	.	.	.	C	-0.32	.	.	F	0.89	0.48
Val	626	.	A	B	.	.	.	.	-0.19	*	.	.	0.03	0.34
Glu	627	.	A	B	.	.	.	.	0.16	*	.	.	-0.18	0.34
Trp	628	.	A	B	.	.	.	.	0.26	*	.	.	-0.09	0.67
Ile	629	.	.	B	.	.	.	.	-0.12	*	.	.	-0.25	1.42
Pro	630	.	.	B	.	.	T	.	0.12	*	.	.	0.10	0.83
Lys	631	.	.	.	.	T	T	.	0.12	*	.	.	0.20	0.78
Tyr	632	.	.	.	.	T	T	.	-0.18	*	.	.	0.20	0.82
Ala	633	.	.	.	.	T	T	.	-0.10	*	.	.	0.84	0.71
Gly	634	.	.	.	.	T	.	.	0.83	*	.	.	0.98	0.55
Val	635	.	.	B	.	.	.	.	1.04	.	*	.	0.92	0.70
Ser	636	.	.	B	.	.	T	.	1.11	.	*	F	2.66	1.17

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Pro	637	.	.	.	.	T	T	.	0.69	.	*	F	3.40	2.31
Lys	638	.	.	.	.	T	T	.	1.32	.	*	F	3.06	1.67
Asp	639	.	.	.	.	T	T	.	0.86	.	*	F	2.72	2.49
Arg	640	A	A	.	.	.	.	.	0.82	.	*	F	1.58	1.33
Cys	641	A	A	.	.	.	.	.	0.46	*	*	F	1.09	0.46
Lys	642	.	A	B	.	.	.	.	0.67	*	*	.	0.30	0.15
Leu	643	.	A	B	.	.	.	.	0.03	.	*	.	0.30	0.13
Ile	644	.	A	B	.	.	.	.	0.08	.	*	.	-0.60	0.25
Cys	645	.	A	B	.	.	.	.	-0.38	.	*	.	0.30	0.25
Gln	646	.	A	B	.	.	.	.	-0.60	*	*	.	-0.30	0.30
Ala	647	.	A	B	.	.	.	.	-0.99	*	*	.	-0.30	0.30
Lys	648	.	A	B	.	.	.	.	-0.42	*	*	F	-0.15	0.55
Gly	649	.	.	.	.	T	T	.	-0.23	*	.	F	0.65	0.50
Ile	650	.	.	.	.	T	T	.	-0.27	.	*	.	0.20	0.43
Gly	651	.	.	B	.	.	T	.	-1.12	.	*	.	-0.20	0.18
Tyr	652	.	.	B	.	.	T	.	-1.34	.	.	.	-0.20	0.14
Phe	653	.	.	B	B	.	.	.	-1.39	.	.	.	-0.60	0.16
Phe	654	.	.	B	B	.	.	.	-1.26	.	*	.	-0.60	0.29
Val	655	.	.	B	B	.	.	.	-0.32	.	*	.	-0.60	0.28
Leu	656	.	.	B	B	.	.	.	-0.83	.	*	.	-0.60	0.65
Gln	657	.	.	B	.	.	T	.	-1.44	.	.	.	-0.20	0.56
Pro	658	.	.	B	.	.	T	.	-0.74	*	.	F	-0.05	0.56

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Lys	659	.	.	.	.	T	T	.	-0.39	.	*	F	1.40	1.13
Val	660	.	.	B	.	.	T	.	0.16	.	.	F	0.85	0.65
Val	661	.	.	B	.	.	T	.	0.76	.	*	F	0.85	0.60
Asp	662	.	.	B	.	.	T	.	0.09	.	.	F	1.06	0.47
Gly	663	.	.	B	.	.	T	.	0.00	*	.	F	0.67	0.34
Thr	664	.	.	B	.	.	T	.	-0.26	*	.	F	1.48	0.61
Pro	665	.	.	B	.	.	.	.	0.60	.	.	F	1.49	0.56
Cys	666	.	.	.	.	T	.	.	1.16	.	.	F	2.10	0.95
Ser	667	.	.	.	.	.	T	C	0.84	.	.	F	1.89	0.88
Pro	668	.	.	.	.	T	T	.	0.89	.	.	F	1.88	0.82
Asp	669	.	.	.	.	T	T	.	0.34	.	.	F	1.82	2.06
Ser	670	.	.	.	.	T	T	.	-0.11	.	.	F	1.61	1.14
Thr	671	.	.	.	B	T	.	.	-0.30	.	*	F	0.85	0.39
Ser	672	.	.	B	B	.	.	.	0.00	.	*	F	-0.15	0.18
Val	673	.	.	B	B	.	.	.	-0.13	.	*	.	-0.60	0.23
Cys	674	.	.	B	B	.	.	.	-0.13	.	*	.	-0.60	0.16
Val	675	.	.	B	B	.	.	.	-0.50	.	*	.	-0.60	0.20
Gln	676	.	.	B	B	.	.	.	-1.04	.	*	F	-0.45	0.15
Gly	677	.	.	B	B	.	.	.	-0.70	.	*	F	-0.45	0.20
Gln	678	.	.	B	B	.	.	.	-0.43	.	*	F	-0.15	0.54
Cys	679	.	.	B	B	.	.	.	-0.11	.	.	.	0.30	0.32
Val	680	.	.	B	B	.	.	.	0.08	*	*	.	0.30	0.32

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Lys	681	.	.	B	.	.	T	.	0.08	*	.	.	0.10	0.10
Ala	682	.	.	B	.	.	T	.	0.53	*	.	.	0.70	0.30
Gly	683	.	.	B	.	.	T	.	-0.36	*	.	.	1.00	0.80
Cys	684	.	.	B	.	.	T	.	-0.58	*	.	.	1.00	0.28
Asp	685	A	.	.	B	.	.	.	0.28	*	.	.	0.30	0.20
Arg	686	A	.	.	B	.	.	.	-0.07	*	.	.	0.60	0.33
Ile	687	A	.	.	B	.	.	.	0.57	*	.	.	0.60	0.82
Ile	688	A	.	.	B	.	.	.	0.96	*	.	F	0.75	0.99
Asp	689	A	.	.	.	.	T	.	1.67	*	*	F	1.30	1.01
Ser	690	A	.	.	.	.	T	.	0.97	*	*	F	1.30	2.88
Lys	691	A	.	.	.	.	T	.	0.86	*	.	F	1.61	3.55
Lys	692	.	.	.	.	T	T	.	1.79	*	*	F	2.32	3.55
Lys	693	.	.	.	.	T	.	.	2.01	*	*	F	2.43	5.30
Phe	694	.	.	.	.	T	.	.	1.67	*	*	F	2.74	1.42
Asp	695	.	.	.	.	T	T	.	1.11	*	.	F	3.10	0.70
Lys	696	.	.	B	.	.	T	.	0.40	*	.	F	2.39	0.26
Cys	697	.	.	B	.	.	T	.	0.01	*	.	.	1.63	0.16
Gly	698	.	.	B	.	.	T	.	-0.38	*	.	.	1.32	0.10
Val	699	.	.	B	.	.	.	.	0.32	*	.	.	0.21	0.05
Cys	700	.	.	.	.	T	.	.	-0.02	.	.	.	0.00	0.14
Gly	701	.	.	.	.	T	T	.	-0.37	.	.	F	0.65	0.14
Gly	702	.	.	.	.	T	T	.	-0.01	.	.	F	0.65	0.26

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asn	703	.	.	.	.	T	T	.	-0.33	.	.	F	0.65	0.69
Gly	704	.	.	.	.	T	T	.	0.57	.	.	F	0.65	0.37
Ser	705	.	.	.	.	T	T	.	1.28	.	.	F	1.25	0.76
Thr	706	.	.	B	.	.	T	.	0.73	.	.	F	1.41	0.94
Cys	707	.	.	B	.	.	T	.	0.78	.	*	F	1.37	0.67
Lys	708	.	.	B	.	.	T	.	0.43	.	*	F	1.63	0.67
Lys	709	.	.	B	.	.	.	.	0.48	*	*	F	1.69	0.46
Ile	710	.	.	B	.	.	T	.	-0.08	*	*	F	2.60	1.14
Ser	711	.	.	B	.	.	T	.	-0.08	*	*	F	1.89	0.42
Gly	712	.	.	B	.	.	T	.	0.29	*	*	F	1.03	0.31
Ser	713	.	.	B	.	.	T	.	-0.34	*	*	F	0.77	0.58
Val	714	.	.	B	B	.	.	.	-0.34	.	*	F	0.11	0.44
Thr	715	.	.	B	B	.	.	.	0.33	.	.	F	0.73	0.89
Ser	716	.	.	B	B	.	.	.	0.29	.	.	F	1.16	1.03
Ala	717	.	.	B	.	.	.	.	0.39	.	.	F	1.64	1.37
Lys	718	.	.	.	.	.	T	C	0.66	.	.	F	2.32	1.49
Pro	719	.	.	.	.	T	T	.	1.51	*	.	F	2.80	1.51
Gly	720	.	.	.	.	T	T	.	0.93	*	.	F	2.52	2.50
Tyr	721	.	.	B	.	.	T	.	0.34	*	.	.	1.54	0.88
His	722	.	.	B	B	.	.	.	0.62	*	.	.	-0.04	0.40
Asp	723	.	.	B	B	.	.	.	-0.31	*	.	.	-0.32	0.58
Ile	724	.	.	B	B	.	.	.	-0.31	*	.	.	-0.60	0.26

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ile	725	.	.	B	B	.	.	.	-0.28	*	.	.	-0.60	0.29
Thr	726	.	.	B	B	.	.	.	-0.38	*	.	.	-0.60	0.25
Ile	727	.	.	B	.	.	T	.	-0.93	*	.	.	-0.20	0.36
Pro	728	.	.	B	.	.	T	.	-1.24	*	.	F	-0.05	0.52
Thr	729	.	.	.	.	.	T	C	-0.36	*	.	F	0.15	0.52
Gly	730	.	.	.	.	.	T	C	-0.36	.	*	F	0.30	1.19
Ala	731	.	.	.	B	.	.	C	-0.04	.	*	F	-0.25	0.54
Thr	732	.	.	.	B	.	.	C	-0.01	.	*	F	0.65	0.65
Asn	733	.	.	B	B	.	.	.	0.24	.	*	F	-0.15	0.48
Ile	734	.	.	B	B	.	.	.	0.56	.	*	F	0.45	0.96
Glu	735	.	.	B	B	.	.	.	1.01	.	*	F	0.60	1.15
Val	736	.	.	B	B	.	.	.	1.60	.	*	F	0.90	1.40
Lys	737	.	.	B	B	.	.	.	1.91	.	*	F	1.24	3.21
Gln	738	.	.	B	.	.	.	.	2.02	.	*	F	1.78	3.21
Arg	739	.	.	B	.	.	.	.	2.57	*	*	F	2.12	8.48
Asn	740	.	.	B	.	.	T	.	2.27	*	*	F	2.66	4.20
Gln	741	.	.	.	.	T	T	.	3.23	*	*	F	3.40	3.25
Arg	742	.	.	.	.	T	T	.	3.19	*	.	F	3.06	3.25
Gly	743	.	.	.	.	T	T	.	3.19	*	.	F	3.00	3.25
Ser	744	.	.	.	.	T	.	.	2.73	*	.	F	2.74	3.02
Arg	745	.	.	.	.	.	.	C	2.43	*	*	F	2.48	1.52
Asn	746	.	.	.	.	T	T	.	1.73	*	.	F	2.82	2.06

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asn	747	.	.	.	.	T	T	.	0.81	*	.	F	2.80	1.33
Gly	748	.	.	.	.	.	T	C	0.57	.	*	F	1.57	0.56
Ser	749	.	.	B	.	.	T	.	-0.02	.	*	F	0.79	0.35
Phe	750	.	A	B	.	.	.	.	-0.09	.	*	.	-0.04	0.15
Leu	751	.	A	B	.	.	.	.	-0.68	.	.	.	-0.32	0.31
Ala	752	.	A	B	.	.	.	.	-1.27	*	.	.	-0.60	0.23
Ile	753	.	A	B	.	.	.	.	-0.92	.	.	.	-0.60	0.27
Lys	754	A	A	.	.	.	.	.	-0.97	.	.	.	0.30	0.55
Ala	755	A	A	.	.	.	.	.	-0.58	.	.	.	0.30	0.54
Ala	756	A	A	.	.	.	.	.	-0.01	.	.	F	0.60	1.12
Asp	757	A	.	.	.	.	T	.	-0.31	.	.	F	0.85	0.87
Gly	758	.	.	B	.	.	T	.	-0.23	.	*	F	0.25	0.61
Thr	759	.	.	B	.	.	T	.	-0.28	.	.	F	-0.05	0.50
Tyr	760	.	.	B	.	.	T	.	-0.03	.	*	.	-0.20	0.48
Ile	761	.	.	B	.	.	.	.	0.56	.	*	.	-0.40	0.48
Leu	762	.	.	B	.	.	.	.	0.31	.	*	.	-0.40	0.55
Asn	763	.	.	B	.	.	T	.	0.34	.	*	F	-0.50	0.55
Gly	764	.	.	.	.	T	T	.	-0.16	.	*	F	0.50	1.14
Asp	765	.	.	.	.	T	T	.	-0.21	.	*	F	0.50	1.14
Tyr	766	.	.	.	.	.	T	C	0.37	.	*	F	0.45	0.95
Thr	767	.	.	B	B	.	.	.	0.37	.	*	.	-0.15	1.38
Leu	768	.	.	B	B	.	.	.	0.37	*	*	.	-0.60	0.68

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ser	769	.	.	B	B	.	.	.	0.71	*	.	F	-0.45	0.75
Thr	770	.	.	B	B	.	.	.	0.71	*	*	F	-0.15	0.90
Leu	771	A	.	.	B	.	.	.	0.07	*	.	F	0.60	1.83
Glu	772	A	.	.	B	.	.	.	-0.22	*	.	F	0.45	0.96
Gln	773	A	.	.	B	.	.	.	0.34	*	*	F	0.45	0.66
Asp	774	A	.	.	B	.	.	.	0.69	.	*	F	0.00	1.25
Ile	775	A	.	.	B	.	.	.	0.66	.	*	.	0.75	1.44
Met	776	A	.	.	B	.	.	.	0.61	.	*	.	0.30	0.82
Tyr	777	.	.	B	B	.	.	.	-0.24	.	*	.	-0.30	0.37
Lys	778	.	.	B	B	.	.	.	-1.06	.	*	.	-0.60	0.39
Gly	779	.	.	B	B	.	.	.	-0.94	.	*	.	-0.60	0.32
Val	780	.	.	B	B	.	.	.	-0.30	.	*	.	-0.30	0.40
Val	781	.	.	B	B	.	.	.	0.00	.	*	.	-0.30	0.32
Leu	782	.	.	B	B	.	.	.	-0.10	.	*	.	-0.60	0.43
Arg	783	.	.	B	B	.	.	.	-0.44	.	*	.	-0.60	0.57
Tyr	784	.	.	B	.	.	T	.	-0.40	*	*	.	0.25	1.03
Ser	785	.	.	.	.	T	T	.	-0.13	.	*	F	0.80	1.68
Gly	786	.	.	.	.	.	T	C	0.13	*	*	F	1.05	0.86
Ser	787	.	.	.	.	.	T	C	0.13	.	*	F	0.45	0.56
Ser	788	.	A	.	.	.	.	C	0.02	.	*	F	0.05	0.34
Ala	789	A	A	.	.	.	.	.	0.38	*	.	F	0.45	0.60
Ala	790	A	A	.	.	.	.	.	-0.21	*	*	.	0.60	0.88

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	791	A	A	.	.	.	.	.	0.24	*	*	.	0.30	0.46
Glu	792	A	A	.	.	.	.	.	0.24	*	*	.	0.60	0.89
Arg	793	.	A	B	B	.	.	.	-0.16	*	*	F	0.90	1.18
Ile	794	A	A	.	B	.	.	.	0.13	*	*	F	0.60	1.24
Arg	795	A	A	.	B	.	.	.	0.51	*	*	F	0.75	0.96
Ser	796	.	A	.	.	T	.	.	0.51	.	*	F	1.13	0.76
Phe	797	.	.	.	.	.	.	C	0.56	.	*	F	0.81	0.89
Ser	798	.	.	.	.	.	T	C	0.44	.	*	F	1.89	0.91
Pro	799	.	.	.	.	.	T	C	1.12	*	*	F	2.32	1.17
Leu	800	.	.	.	.	T	T	.	0.20	*	*	F	2.80	2.10
Lys	801	.	.	.	.	.	T	C	0.19	*	*	F	2.32	1.29
Glu	802	.	.	.	.	.	.	C	0.00	.	*	F	1.84	1.20
Pro	803	A	.	.	B	.	.	.	0.30	.	*	F	1.16	1.02
Leu	804	A	.	.	B	.	.	.	-0.34	.	*	F	0.73	0.89
Thr	805	.	.	B	B	.	.	.	-0.34	.	*	.	-0.30	0.38
Ile	806	.	.	B	B	.	.	.	-0.70	.	*	.	-0.60	0.20
Gln	807	.	.	B	B	.	.	.	-1.56	.	.	.	-0.60	0.35
Val	808	.	.	B	B	.	.	.	-1.69	.	*	.	-0.60	0.18
Leu	809	.	.	B	B	.	.	.	-0.88	.	*	.	-0.60	0.26
Thr	810	.	.	B	B	.	.	.	-1.16	.	.	.	-0.60	0.24
Val	811	.	.	B	B	.	.	.	-1.08	.	*	.	-0.60	0.33
Gly	812	.	.	B	B	.	.	.	-0.97	*	*	.	-0.60	0.33

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asn	813	A	.	.	.	.	.	.	-0.32	*	*	.	0.12	0.44
Ala	814	A	.	.	.	.	.	.	0.53	*	*	.	0.34	0.92
Leu	815	A	.	.	.	.	.	.	-0.04	*	*	F	1.76	1.86
Arg	816	.	.	B	.	.	.	.	0.86	*	*	F	1.53	0.81
Pro	817	.	.	B	.	.	.	.	0.96	*	*	F	2.20	1.61
Lys	818	.	.	B	B	.	.	.	0.64	*	*	F	1.48	3.05
Ile	819	.	.	B	B	.	.	.	0.99	.	*	F	1.56	2.25
Lys	820	.	.	B	B	.	.	.	1.10	*	*	F	0.44	2.28
Tyr	821	.	.	B	B	.	.	.	0.13	*	*	.	-0.38	0.99
Thr	822	.	.	B	B	.	.	.	0.39	.	*	.	-0.45	1.04
Tyr	823	A	.	.	B	.	.	.	0.39	.	*	.	-0.45	1.04
Phe	824	A	.	.	B	.	.	.	1.32	.	*	.	-0.45	1.33
Val	825	A	.	.	B	.	.	.	1.32	.	.	.	0.45	1.85
Lys	826	A	.	.	B	.	.	.	1.57	.	.	F	0.90	2.36
Lys	827	A	A	.	.	.	.	.	1.58	*	.	F	0.90	4.71
Lys	828	A	A	.	.	.	.	.	1.12	*	.	F	0.90	8.51
Lys	829	A	A	.	.	.	.	.	1.82	*	.	F	0.90	3.68
Glu	830	A	A	.	.	.	.	.	2.09	*	.	F	0.90	2.96
Ser	831	A	A	.	.	.	.	.	1.16	*	.	F	0.90	1.50
Phe	832	A	A	.	.	.	.	.	0.90	.	.	.	0.30	0.52
Asn	833	.	A	B	.	.	.	.	0.54	*	.	.	-0.30	0.47
Ala	834	.	.	B	.	.	.	.	-0.20	*	*	.	-0.40	0.50

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ile	835	.	.	.	.	.	.	C	-0.50	*	.	.	-0.20	0.50
Pro	836	.	.	.	.	.	T	C	-0.79	.	.	.	0.00	0.42
Thr	837	.	.	.	.	T	T	.	-0.38	*	*	.	0.20	0.42
Phe	838	A	.	.	.	.	T	.	-1.23	*	.	.	-0.20	0.63
Ser	839	.	.	.	.	.	T	C	-1.53	*	.	.	0.00	0.30
Ala	840	.	A	B	B	.	.	.	-0.64	*	.	.	-0.60	0.15
Trp	841	.	A	B	B	.	.	.	-0.43	.	.	.	-0.60	0.29
Val	842	A	A	.	B	.	.	.	-0.41	.	.	.	-0.30	0.38
Ile	843	A	A	.	B	.	.	.	-0.06	*	.	.	-0.60	0.40
Glu	844	A	A	.	B	.	.	.	0.24	*	.	.	-0.60	0.37
Glu	845	A	A	.	.	.	.	.	0.17	*	.	.	0.30	0.87
Trp	846	A	A	.	.	.	.	.	0.16	*	.	.	0.61	0.66
Gly	847	A	A	.	.	.	.	.	1.06	*	.	F	1.37	0.51
Glu	848	.	A	.	.	T	.	.	1.64	*	.	F	2.08	0.59
Cys	849	.	A	.	.	T	.	.	0.98	*	.	F	2.09	0.76
Ser	850	.	.	.	.	T	T	.	0.98	.	.	F	3.10	0.41
Lys	851	.	.	.	.	T	T	.	0.46	.	.	F	2.79	0.41
Ser	852	.	.	.	.	T	T	.	0.46	.	.	F	2.18	0.63
Cys	853	.	.	.	.	T	T	.	0.17	*	*	.	2.02	0.47
Glu	854	A	A	.	.	.	.	.	0.83	*	.	.	0.61	0.24
Leu	855	A	A	.	.	.	.	.	1.24	.	.	.	-0.30	0.32
Gly	856	.	A	.	.	.	.	.	1.31	.	*	.	0.85	1.16

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Trp	857	A	A	.	.	.	.	.	0.80	*	*	.	0.75	1.31
Gln	858	A	A	.	.	.	.	.	0.61	*	*	.	-0.15	1.31
Arg	859	A	A	.	.	.	.	.	0.61	*	*	.	-0.30	0.98
Arg	860	.	A	B	.	.	.	.	0.76	.	*	.	0.45	1.61
Leu	861	.	A	B	.	.	.	.	1.21	*	.	.	0.60	0.50
Val	862	.	A	B	.	.	.	.	1.50	*	.	.	0.60	0.50
Glu	863	.	A	B	.	.	.	.	0.61	.	.	.	0.94	0.43
Cys	864	.	A	B	.	.	.	.	0.50	.	.	.	0.98	0.36
Arg	865	.	A	.	.	T	.	.	0.04	.	.	F	2.17	0.78
Asp	866	.	.	.	.	T	T	.	0.86	.	.	F	2.91	0.45
Ile	867	.	.	.	.	T	T	.	1.50	.	.	F	3.40	1.45
Asn	868	.	.	.	.	T	T	.	0.91	.	.	F	3.06	1.14
Gly	869	.	.	.	.	.	T	C	1.28	.	.	F	2.07	0.69
Gln	870	.	.	.	.	.	T	C	1.17	.	*	F	1.28	1.32
Pro	871	.	.	.	.	.	T	C	0.50	.	*	F	1.54	1.42
Ala	872	.	.	.	.	.	T	C	0.80	.	*	F	1.05	0.77
Ser	873	A	.	.	.	.	T	.	0.84	*	.	F	0.85	0.45
Glu	874	A	A	.	.	.	.	.	1.19	*	.	F	0.75	0.58
Cys	875	A	A	.	.	.	.	.	0.33	*	.	.	0.60	1.00
Ala	876	A	A	.	.	.	.	.	0.59	*	.	.	0.60	0.55
Lys	877	A	A	.	.	.	.	.	0.97	*	.	F	0.75	0.64
Glu	878	A	A	.	.	.	.	.	0.68	*	.	F	0.90	1.84

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Val	879	A	A	.	.	.	.	.	0.38	*	.	F	0.90	1.84
Lys	880	A	A	.	.	.	.	.	0.73	*	.	F	0.90	1.23
Pro	881	A	.	.	.	.	T	.	1.43	*	.	F	1.30	1.03
Ala	882	.	.	.	.	T	T	.	1.18	*	.	F	2.01	2.71
Ser	883	.	.	.	.	T	T	.	0.51	.	*	F	2.32	2.10
Thr	884	.	.	.	.	T	T	.	0.78	.	*	F	2.18	0.73
Arg	885	.	.	B	.	.	T	.	0.73	.	*	F	2.09	0.73
Pro	886	.	.	.	.	T	T	.	0.91	.	*	F	3.10	0.91
Cys	887	.	.	.	.	T	T	.	1.29	.	*	.	2.64	0.85
Ala	888	.	.	.	.	T	T	.	0.92	.	*	.	2.43	0.67
Asp	889	.	.	.	.	T	.	.	1.02	.	*	.	1.72	0.23
His	890	.	.	.	.	.	T	C	0.91	.	*	.	1.51	0.67
Pro	891	.	.	.	.	T	T	.	0.83	.	.	.	1.65	1.16
Cys	892	.	.	.	.	T	T	.	1.50	.	*	.	1.00	0.73
Pro	893	.	.	.	.	T	T	.	1.28	.	*	.	0.60	0.93
Gln	894	.	A	.	.	T	.	.	0.93	.	.	.	0.10	0.49
Trp	895	.	A	B	.	.	.	.	0.97	.	.	.	-0.40	0.91
Gln	896	.	A	B	.	.	.	.	0.89	.	.	.	-0.05	1.02
Leu	897	.	A	B	.	.	.	.	1.26	.	.	.	-0.60	0.62
Gly	898	.	.	.	.	T	.	.	1.17	.	.	.	0.00	0.79
Glu	899	.	.	.	.	T	.	.	0.50	.	.	F	0.45	0.61
Trp	900	.	.	.	.	T	.	.	0.49	.	.	F	0.45	0.40

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Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ser	901	.	.	.	.	T	T	.	0.53	.	.	F	0.65	0.54
Ser	902	.	.	.	.	T	T	.	1.03	.	.	F	1.25	0.62
Cys	903	.	.	.	.	T	T	.	0.71	.	*	F	0.65	0.85
Ser	904	.	.	.	.	T	T	.	0.37	*	*	F	1.25	0.34
Lys	905	.	.	.	.	T	.	.	0.70	*	*	F	1.05	0.25
Thr	906	.	.	.	.	T	.	.	0.66	*	*	F	1.69	0.94
Cys	907	.	.	.	.	T	.	.	0.71	*	.	F	2.03	0.69
Gly	908	.	.	.	.	T	T	.	1.42	*	*	F	2.27	0.54
Lys	909	.	.	.	.	T	T	.	1.77	*	*	F	2.61	0.75
Gly	910	.	.	.	.	T	T	.	1.83	*	*	F	3.40	2.81
Tyr	911	.	.	.	.	T	T	.	1.84	.	.	F	3.06	5.57
Lys	912	.	A	B	.	.	.	.	1.70	*	.	F	1.92	3.73
Lys	913	.	A	B	.	.	.	.	2.09	*	.	F	1.58	3.11
Arg	914	.	A	B	.	.	.	.	1.38	*	.	F	1.24	3.97
Ser	915	.	A	B	.	.	.	.	0.91	*	.	F	0.90	1.06
Leu	916	.	A	B	.	.	.	.	0.86	*	.	F	0.75	0.44
Lys	917	.	A	B	.	.	.	.	0.78	*	.	.	0.30	0.30
Cys	918	.	A	B	.	.	.	.	0.73	*	.	.	-0.30	0.30
Leu	919	.	A	B	.	.	.	.	0.28	*	.	.	0.30	0.62
Ser	920	.	.	B	.	.	.	.	0.23	.	.	.	0.50	0.31
His	921	.	.	B	.	.	T	.	0.19	*	.	F	0.85	0.56
Asp	922	.	.	.	.	T	T	.	-0.67	*	.	F	0.65	0.51

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	923	.	.	.	.	T	T	.	-0.30	.	.	F	0.65	0.31
Gly	924	.	.	.	.	T	T	.	0.48	.	.	F	0.65	0.31
Val	925	.	.	B	.	.	.	.	0.78	.	.	.	-0.10	0.25
Leu	926	.	.	B	.	.	.	.	0.51	.	.	.	-0.10	0.44
Ser	927	.	.	B	.	.	.	.	-0.16	.	.	.	-0.10	0.59
His	928	.	.	B	.	.	T	.	0.19	.	.	.	0.10	0.43
Glu	929	.	.	B	.	.	T	.	0.32	.	.	F	0.85	0.87
Ser	930	A	.	.	.	.	T	.	0.37	*	.	F	1.30	1.00
Cys	931	A	.	.	.	.	T	.	1.22	*	.	F	0.85	0.61
Asp	932	A	.	.	.	.	T	.	1.57	*	.	F	1.15	0.70
Pro	933	A	.	.	.	.	T	.	1.39	*	.	F	1.30	1.05
Leu	934	A	.	.	.	.	T	.	1.43	*	.	F	1.30	3.02
Lys	935	A	.	.	.	.	T	.	1.70	*	.	F	1.30	3.62
Lys	936	A	A	.	.	.	.	.	1.67	*	.	F	0.90	3.18
Pro	937	A	A	.	.	.	.	.	0.78	*	.	F	0.90	3.34
Lys	938	A	A	.	.	.	.	.	0.99	*	*	F	0.90	1.17
His	939	A	A	.	.	.	.	.	1.10	*	*	.	0.60	0.98
Phe	940	.	A	B	.	.	.	.	0.39	*	*	.	-0.30	0.55
Ile	941	.	A	B	.	.	.	.	0.03	*	*	.	-0.30	0.15
Asp	942	A	A	.	.	.	.	.	-0.36	*	*	.	-0.60	0.16
Phe	943	A	A	.	.	.	.	.	-0.99	*	*	.	-0.60	0.18
Cys	944	A	A	.	.	.	.	.	-0.96	.	.	.	-0.60	0.26

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Res	Pos.	Garni... Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni... Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen.. Alpha	Eisen.. Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Thr	945	A	A	.	.	.	.	.	-0.92	.	*	.	0.30	0.27
Met	946	A	A	.	.	.	.	.	-0.33	.	*	.	-0.60	0.16
Ala	947	A	A	.	.	.	.	.	-0.72	.	.	.	-0.30	0.41
Glu	948	A	A	.	.	.	.	.	-0.41	.	.	.	0.30	0.36
Cys	949	A	A	.	.	.	.	.	-0.13	.	.	.	0.30	0.47
Ser	950	A	A	.	.	.	.	.	-0.21	.	.	.	0.30	0.60

Table 2

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Met	1	.	.	B	.	.	.	.	-0.37	.	.	.	-0.40	0.50
Phe	2	.	.	B	.	.	.	.	-0.57	.	.	.	-0.40	0.61
Pro	3	.	.	B	.	.	.	.	-0.77	.	.	.	-0.40	0.48
Ala	4	.	.	.	.	.	.	C	-0.59	.	*	.	-0.20	0.49
Pro	5	.	.	.	.	.	.	C	-0.09	.	*	.	-0.20	0.87
Ala	6	.	.	.	.	.	.	C	0.22	*	*	.	0.85	1.11
Ala	7	.	.	.	.	.	T	C	0.11	*	*	.	0.45	1.15
Pro	8	A	.	.	.	.	T	.	0.11	*	.	.	-0.20	0.61
Arg	9	.	.	.	.	T	T	.	0.00	*	.	.	0.20	0.94
Trp	10	.	.	B	.	.	T	.	-0.60	*	.	.	-0.20	0.81
Leu	11	.	A	B	.	.	.	.	-0.82	*	.	.	-0.60	0.43
Pro	12	.	A	B	.	.	.	.	-1.04	*	.	.	-0.60	0.18
Phe	13	.	A	B	.	.	.	.	-1.64	*	.	.	-0.60	0.14
Leu	14	A	A	.	.	.	.	.	-2.57	*	.	.	-0.60	0.14
Leu	15	A	A	.	.	.	.	.	-3.09	.	.	.	-0.60	0.08
Leu	16	A	A	.	.	.	.	.	-3.09	.	.	.	-0.60	0.07
Leu	17	A	A	.	.	.	.	.	-3.69	.	.	.	-0.60	0.07
Leu	18	A	A	.	.	.	.	.	-3.80	.	.	.	-0.60	0.07
Leu	19	A	A	.	.	.	.	.	-3.20	.	.	.	-0.60	0.07
Leu	20	A	A	.	.	.	.	.	-3.20	.	.	.	-0.60	0.14

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	21	A	A	.	.	.	.	.	-2.98	*	.	.	-0.60	0.14
Leu	22	.	A	B	.	.	.	.	-2.06	*	.	.	-0.60	0.17
Pro	23	.	A	B	.	.	.	.	-1.59	*	.	.	-0.60	0.39
Leu	24	A	A	.	.	.	.	.	-1.37	*	.	.	-0.60	0.47
Ala	25	A	A	.	.	.	.	.	-0.77	*	.	.	-0.04	0.58
Arg	26	.	A	B	.	.	.	.	-0.54	*	.	.	0.82	0.58
Gly	27	.	A	B	.	.	.	.	0.38	.	.	F	0.63	0.71
Ala	28	.	.	B	.	.	.	.	0.38	.	.	F	2.14	1.37
Pro	29	.	.	.	.	.	.	C	0.60	.	.	F	2.60	1.08
Ala	30	.	.	B	.	.	.	.	0.60	.	.	F	1.84	1.11
Arg	31	.	.	B	.	.	.	.	0.14	.	.	F	1.58	1.11
Pro	32	.	.	B	.	.	.	.	0.14	.	*	F	1.17	0.71
Ala	33	.	.	B	.	.	T	.	0.73	.	*	F	1.11	0.69
Ala	34	A	.	.	.	.	T	.	0.36	.	*	F	0.85	0.61
Gly	35	.	.	.	.	.	T	C	0.64	.	*	F	0.45	0.40
Gly	36	.	.	.	.	.	T	C	0.53	.	*	F	0.45	0.53
Gln	37	A	.	.	.	.	.	.	-0.07	.	.	F	0.65	0.91
Ala	38	.	.	B	.	.	.	.	-0.33	.	.	F	0.65	0.76
Ser	39	.	.	B	B	B	.	.	-0.60	.	.	F	-0.15	0.57
Glu	40	.	.	B	B	B	.	.	-0.47	.	.	F	-0.15	0.24
Leu	41	.	.	B	B	B	.	.	-0.43	.	*	.	-0.30	0.37
Val	42	.	.	B	B	B	.	.	-0.32	.	*	.	-0.30	0.40

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Val	43	.	.	B	B	B	.	.	-0.54	.	*	.	0.30	0.46
Pro	44	.	.	B	B	B	.	.	-0.46	.	*	F	-0.24	0.46
Thr	45	.	.	B	B	B	.	.	-0.80	.	*	F	0.27	0.95
Arg	46	.	.	B	B	B	.	.	-0.29	.	*	F	0.63	1.26
Leu	47	.	.	.	.	.	T	C	-0.02	.	*	F	2.04	1.10
Pro	48	.	.	.	.	.	T	C	0.49	*	*	F	2.10	0.77
Gly	49	.	.	.	.	.	T	C	0.70	*	*	F	1.89	0.39
Ser	50	.	.	.	.	.	T	C	0.20	*	*	F	1.68	0.81
Ala	51	A	A	.	.	.	.	.	-0.50	*	*	F	0.87	0.43
Gly	52	A	A	.	.	.	.	.	-0.50	.	.	F	0.66	0.44
Glu	53	A	A	.	.	.	.	.	-0.32	.	*	.	-0.30	0.27
Leu	54	A	A	.	.	.	.	.	-0.79	.	*	.	-0.30	0.37
Ala	55	A	A	.	.	.	.	.	-0.79	.	*	.	-0.60	0.31
Leu	56	A	A	.	.	.	.	.	-0.79	.	*	.	-0.60	0.24
His	57	A	A	.	.	.	.	.	-1.14	.	*	.	-0.60	0.29
Leu	58	A	A	.	.	.	.	.	-1.49	*	*	.	-0.60	0.25
Ser	59	A	A	.	.	.	.	.	-0.63	*	*	.	-0.60	0.30
Ala	60	A	A	.	.	.	.	.	-0.39	*	*	.	-0.30	0.44
Phe	61	A	A	.	.	.	.	.	-0.28	*	*	.	-0.30	0.53
Gly	62	.	.	.	.	T	T	.	-1.10	*	.	.	0.50	0.34
Lys	63	A	.	.	.	.	T	.	-1.10	.	*	F	-0.05	0.25
Gly	64	.	.	B	.	.	T	.	-0.69	.	*	.	-0.20	0.24

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Phe	65	.	.	B	.	.	T	.	-0.91	.	*	.	0.70	0.47
Val	66	.	.	B	B	.	.	.	-0.80	*	*	.	-0.30	0.19
Leu	67	.	.	B	B	.	.	.	-0.67	*	*	.	-0.30	0.20
Arg	68	.	.	B	B	.	.	.	-0.71	.	*	.	0.00	0.35
Leu	69	.	.	B	B	.	.	.	-0.37	*	*	.	1.20	0.80
Ala	70	.	.	.	.	.	T	C	0.03	.	*	.	2.55	1.61
Pro	71	.	.	.	.	.	T	C	0.19	*	*	F	3.00	1.10
Asp	72	.	.	.	.	T	T	.	0.19	.	*	F	2.60	1.16
Asp	73	A	.	.	.	.	T	.	-0.51	.	*	F	1.75	0.95
Ser	74	A	A	.	.	.	.	.	0.09	.	.	.	0.90	0.62
Phe	75	A	A	.	.	.	.	.	0.68	.	.	.	0.60	0.57
Leu	76	A	A	.	.	.	.	.	0.19	.	*	.	0.30	0.59
Ala	77	A	A	.	.	.	.	.	0.23	.	*	.	-0.60	0.38
Pro	78	A	A	.	.	.	.	.	-0.66	.	*	.	-0.30	0.89
Glu	79	A	A	.	.	.	.	.	-0.36	*	*	F	-0.15	0.75
Phe	80	A	A	.	.	.	.	.	0.46	*	.	F	0.90	1.29
Lys	81	A	A	.	.	.	.	.	0.46	*	*	F	0.90	1.63
Ile	82	A	A	.	.	.	.	.	0.70	*	.	F	0.75	0.78
Glu	83	A	A	.	.	.	.	.	0.57	*	*	F	0.45	0.89
Arg	84	A	A	.	.	.	.	.	0.27	*	*	F	0.75	0.44
Leu	85	.	A	.	.	T	.	.	0.62	*	*	F	0.85	0.84
Gly	86	.	A	.	.	T	.	.	0.69	*	*	F	1.15	0.48

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	87	.	.	.	.	.	T	C	0.99	*	*	F	1.35	0.48
Ser	88	.	.	.	.	.	T	C	0.68	*	*	F	1.05	0.59
Gly	89	.	.	.	.	.	T	C	0.22	*	*	F	1.05	0.86
Arg	90	.	.	B	.	.	T	.	0.69	.	*	F	1.19	0.86
Ala	91	.	.	.	.	.	T	C	1.03	.	*	F	1.73	0.63
Thr	92	.	.	B	.	.	T	.	1.49	.	*	F	2.32	1.11
Gly	93	.	.	B	.	.	T	.	1.44	.	*	F	2.66	1.11
Gly	94	.	.	.	.	T	T	.	0.98	*	*	F	3.40	1.09
Glu	95	.	.	B	.	.	.	.	0.98	*	*	F	2.31	0.62
Arg	96	.	.	B	.	.	.	.	1.22	*	.	F	2.12	1.23
Gly	97	.	.	.	.	T	.	.	0.87	*	*	F	2.18	1.23
Leu	98	.	.	B	.	.	T	.	0.51	*	.	F	1.49	0.38
Arg	99	.	.	B	.	.	T	.	0.16	*	.	.	0.70	0.17
Gly	100	.	.	B	.	.	T	.	-0.14	*	.	.	-0.20	0.15
Cys	101	.	.	B	.	.	T	.	-0.60	*	.	.	-0.20	0.24
Phe	102	.	.	B	.	.	.	.	-0.57	.	*	.	-0.10	0.12
Phe	103	.	.	B	.	.	T	.	-0.61	.	*	.	-0.20	0.18
Ser	104	.	.	B	.	.	T	.	-0.72	.	*	F	-0.05	0.24
Gly	105	.	.	.	.	.	T	C	-0.72	.	*	F	0.15	0.45
Thr	106	.	.	.	.	.	T	C	-0.06	*	*	F	0.45	0.52
Val	107	.	.	.	B	.	.	C	0.43	.	*	F	1.25	0.67
Asn	108	.	.	.	B	.	.	C	1.13	.	*	F	1.70	1.05

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	109	.	.	.	B	.	.	C	1.13	.	*	F	2.30	1.26
Glu	110	.	.	.	.	.	T	C	0.67	.	*	F	3.00	2.27
Pro	111	A	.	.	.	.	T	.	0.39	.	*	F	2.50	1.16
Glu	112	A	.	.	.	.	T	.	0.66	.	*	F	2.20	1.19
Ser	113	A	.	.	.	.	T	.	-0.20	.	.	F	1.75	0.69
Leu	114	A	A	.	B	.	.	.	-0.16	.	.	.	0.00	0.33
Ala	115	A	A	.	B	.	.	.	-0.97	.	.	.	-0.30	0.26
Ala	116	A	A	.	B	.	.	.	-1.42	.	.	.	-0.60	0.16
Val	117	A	A	.	B	.	.	.	-1.31	.	.	.	-0.60	0.10
Ser	118	.	A	B	B	.	.	.	-1.36	*	.	.	-0.30	0.20
Leu	119	.	.	B	B	.	.	.	-1.36	*	.	.	-0.30	0.20
Cys	120	.	.	B	.	.	T	.	-1.07	*	.	.	0.10	0.22
Arg	121	.	.	B	.	.	T	.	-0.82	*	.	.	0.10	0.22
Gly	122	.	.	.	.	T	T	.	-0.27	*	.	F	0.65	0.26
Leu	123	.	.	.	.	T	T	.	-0.67	*	.	F	1.25	0.65
Ser	124	.	.	.	.	.	T	C	-0.67	*	.	F	0.45	0.29
Gly	125	.	.	B	.	.	T	.	-0.81	.	*	F	-0.05	0.24
Ser	126	.	.	B	.	.	T	.	-0.92	.	*	F	-0.05	0.24
Phe	127	.	.	B	.	.	T	.	-0.92	.	*	.	0.10	0.30
Leu	128	.	A	B	.	.	.	C	-0.11	.	*	.	-0.30	0.30
Leu	129	.	A	.	.	.	.	.	0.19	.	*	F	0.65	0.39
Asp	130	A	A	.	.	.	.	.	-0.17	.	.	F	0.45	0.77

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	131	A	A	.	.	.	.	.	-0.18	.	.	F	0.45	0.81
Glu	132	A	A	.	.	.	.	.	-0.37	.	*	F	0.90	1.42
Glu	133	A	A	.	.	.	.	.	0.44	.	*	F	0.75	0.60
Phe	134	A	A	.	.	.	.	.	1.04	.	*	.	0.45	1.04
Thr	135	.	A	B	.	.	.	.	1.04	.	*	.	0.30	0.93
Ile	136	.	.	B	.	.	.	.	1.04	.	*	F	0.05	0.93
Gln	137	.	.	B	.	.	.	.	0.46	.	*	F	-0.10	1.06
Pro	138	.	.	.	.	.	.	C	0.11	.	*	F	0.25	0.75
Gln	139	.	.	.	.	T	.	.	0.47	.	*	F	0.60	1.05
Gly	140	.	.	.	.	.	T	C	0.48	.	*	F	0.45	0.60
Ala	141	.	.	.	.	T	T	.	0.56	.	*	F	1.25	0.52
Gly	142	.	.	.	.	.	T	C	-0.03	.	.	F	0.45	0.25
Gly	143	.	.	.	.	.	T	C	0.18	.	.	F	0.65	0.25
Ser	144	.	.	.	.	.	.	C	-0.03	.	.	F	0.65	0.43
Leu	145	.	.	B	.	.	.	.	0.28	*	.	F	0.65	0.68
Ala	146	.	.	B	.	.	.	.	0.98	*	.	F	0.85	0.93
Gln	147	.	.	B	.	.	T	.	0.51	.	*	F	2.00	1.36
Pro	148	.	.	B	.	.	T	.	0.86	*	.	.	1.05	1.36
His	149	.	.	B	.	.	T	.	1.27	*	.	.	1.45	2.34
Arg	150	.	.	B	.	.	T	.	1.79	*	.	.	1.55	2.64
Leu	151	.	.	B	.	.	.	.	2.03	*	.	.	0.85	1.80
Gln	152	.	.	B	.	.	.	.	1.82	*	.	.	0.65	1.31

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpi... Flexi...	James... Antig...	Emini Surfa...
Arg	153	.	.	.	.	T	.	.	1.44	*	.	.	1.05	1.03
Trp	154	.	.	.	.	T	.	.	1.13	*	.	F	0.84	1.26
Gly	155	.	.	.	.	.	T	C	0.43	*	.	F	0.93	0.72
Pro	156	.	.	.	.	.	T	C	1.36	*	.	F	1.17	0.37
Ala	157	.	.	.	.	T	T	.	1.14	*	.	F	1.61	0.69
Gly	158	.	.	.	.	.	T	C	0.22	*	.	F	2.40	1.08
Ala	159	.	.	.	.	.	.	C	0.30	*	*	F	1.81	0.58
Arg	160	.	.	.B	.	.	.	.	0.76	*	*	F	1.37	0.89
Pro	161	.	.	B	.	.	.	.	0.62	*	*	F	1.58	1.75
Leu	162	.	.	.	.	.	.	C	1.00	*	*	F	1.84	1.72
Pro	163	.	.	.	.	.	.	C	1.34	*	*	F	1.90	1.35
Arg	164	.	.	.	.	.	.	C	1.64	*	*	F	2.20	1.52
Gly	165	.	.	.	.	.	T	C	1.53	*	*	F	2.40	1.93
Pro	166	.	.	.	.	.	T	C	0.89	*	.	F	3.00	2.17
Glu	167	.	.	.	.	.	T	C	1.70	*	.	F	2.55	0.82
Trp	168	A	.	.	.	.	T	.	1.60	*	.	.	2.05	1.44
Glu	169	A	.	.	.	.	.	.	1.14	*	.	.	1.85	1.34
Val	170	A	.	.	.	.	.	.	1.49		.	F	1.85	0.77
Glu	171	A	.	.	.	.	.	.	1.36		*	F	2.00	1.26
Thr	172	A	.	.	.	.	.	.	1.36		*	F	2.15	0.72
Gly	173	.	.	.	.	.	T	C	1.76		.	F	3.00	1.68
Glu	174	A	.	.	.	.	T	.	1.76		.	F	2.50	1.90

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	175	A	.	.	.	.	T	.	2.61		.	F	2.20	2.28
Gln	176	A	.	.	.	.	T	.	2.72		.	F	1.90	4.00
Arg	177	A	A	.	.	.	.	.	2.69		*	F	1.54	4.52
Gln	178	A	A	.	.	.	.	.	3.03		*	F	1.58	4.52
Glu	179	.	A	.	.	T	.	.	3.00	*	*	F	2.32	4.36
Arg	180	.	A	.	.	T	.	.	3.34	*	.	F	2.66	3.03
Gly	181	.	.	.	.	T	T	.	3.34	.	*	F	3.40	3.03
Asp	182	.	.	.	.	.	T	C	3.23	.	.	F	2.86	3.03
His	183	.	.	.	.	.	T	C	2.93	.	*	F	2.52	2.58
Gln	184	.	.	.	.	.	T	C	2.93	.	*	F	2.18	3.50
Glu	185	.	A	.	.	.	.	C	2.82	.	*	F	1.44	3.63
Asp	186	A	A	.	.	.	.	.	3.17	.	.	F	0.90	4.61
Ser	187	A	A	.	.	.	.	.	2.87	.	.	F	0.90	4.61
Glu	188	A	A	.	.	.	.	.	2.90	.	.	F	0.90	3.57
Glu	189	A	A	.	.	.	.	.	2.90	.	.	F	0.90	3.70
Glu	190	A	A	.	.	.	.	.	2.90	.	.	F	0.90	4.79
Ser	191	A	A	.	.	.	.	.	2.90	.	.	F	0.90	4.79
Gln	192	A	A	.	.	.	.	.	2.61	.	.	F	0.90	4.79
Glu	193	A	A	.	.	.	.	.	2.61	.	.	F	0.90	2.79
Glu	194	A	A	.	.	.	.	.	2.27	.	.	F	0.90	3.61
Glu	195	A	A	.	.	.	.	.	1.68	.	.	F	0.90	2.06
Ala	196	A	A	.	.	.	.	.	1.68	.	.	F	1.16	1.20

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Glu	197	A	A	.	.	.	.	.	1.68	.	.	F	1.27	0.93
Gly	198	A	A	.	.	.	.	.	1.47	.	.	F	1.53	0.93
Ala	199	.	A	.	.	T	.	.	1.26	.	.	F	2.34	1.42
Ser	200	.	.	.	.	.	.	C	1.04	.	.	F	2.60	1.27
Glu	201	.	.	.	.	.	.	C	1.42	*	.	F	2.04	1.99
Pro	202	.	.	.	.	.	.	C	0.61	*	.	F	1.78	3.04
Pro	203	.	.	.	.	.	.	C	0.61	.	.	F	1.52	1.87
Pro	204	.	.	.	.	.	T	C	0.61	.	.	F	1.46	1.07
Pro	205	.	.	.	.	.	T	C	0.60	.	.	F	0.45	0.70
Leu	206	.	.	.	.	.	T	C	0.30	*	*	F	0.45	0.65
Gly	207	.	.	B	.	.	T	.	0.62	.	*	F	0.51	0.57
Ala	208	.	.	B	.	.	.	.	0.52	.	*	F	1.17	0.72
Thr	209	.	.	B	.	.	.	.	0.78	*	*	F	1.58	1.25
Ser	210	.	.	B	.	.	T	.	1.10	*	.	F	2.34	2.53
Arg	211	.	.	B	.	.	T	.	1.21	*	.	F	2.60	4.91
Thr	212	.	.	B	.	.	T	.	0.70	*	.	F	2.34	2.95
Lys	213	.	.	B	.	.	T	.	0.99	*	.	F	2.08	1.63
Arg	214	.	.	B	B	.	.	.	1.30	*	.	F	1.42	1.12
Phe	215	.	.	B	B	.	.	.	1.01	*	*	.	1.01	1.34
Val	216	.	.	B	B	.	.	.	1.01	*	*	.	0.60	0.68
Ser	217	A	.	.	B	.	.	.	0.62	*	*	.	0.60	0.68
Glu	218	A	A	.	.	.	.	.	-0.28	*	*	.	-0.30	0.68

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ala	219	A	A	.	B	.	.	.	-0.39	*	*	.	0.30	0.68
Arg	220	A	A	.	B	.	.	.	0.00	*	*	.	0.60	0.87
Phe	221	A	A	.	B	.	.	.	0.04	*	.	.	0.60	0.73
Val	222	A	A	.	B	.	.	.	-0.47	*	*	.	-0.30	0.59
Glu	223	A	A	.	B	.	.	.	-1.32	*	*	.	-0.30	0.25
Thr	224	A	A	.	B	.	.	.	-1.32	*	*	.	-0.60	0.21
Leu	225	A	A	.	B	.	.	.	-1.43	*	*	.	-0.60	0.29
Leu	226	A	A	.	B	.	.	.	-1.32	.	.	.	0.30	0.28
Val	227	A	A	.	B	.	.	.	-0.77	.	.	.	-0.60	0.20
Ala	228	A	A	.	B	.	.	.	-1.37	.	.	.	-0.30	0.32
Asp	229	A	A	.	B	.	.	.	-1.64	.	.	.	-0.30	0.38
Ala	230	A	A	.	.	.	.	.	-1.42	.	.	.	-0.30	0.52
Ser	231	A	A	.	.	.	.	.	-1.31	.	.	.	0.30	0.52
Met	232	A	A	.	.	.	.	.	-0.70	.	.	.	-0.30	0.27
Ala	233	A	A	.	.	.	.	.	-0.46	.	.	.	-0.60	0.42
Ala	234	A	A	.	.	.	.	.	-1.04	.	.	.	-0.60	0.31
Phe	235	A	A	.	.	.	.	.	-0.46	.	.	.	-0.60	0.32
Tyr	236	A	A	.	.	.	.	.	-0.97	.	.	.	-0.60	0.52
Gly	237	A	A	.	.	.	.	.	-0.37	.	.	.	-0.60	0.43
Ala	238	A	A	.	.	.	.	.	0.22	.	.	.	-0.60	0.86
Asp	239	A	A	.	.	.	.	.	0.78	*	*	.	-0.30	0.88
Leu	240	A	A	.	.	.	.	.	0.59	*	.	.	0.45	1.21

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gln	241	A	A	.	B	.	.	.	0.02	*	*	.	-0.30	0.84
Asn	242	A	A	.	B	.	.	.	0.06	*	.	.	-0.30	0.41
His	243	.	A	B	B	.	.	.	-0.17	*	*	.	-0.60	0.72
Ile	244	.	A	B	B	.	.	.	-0.77	*	.	.	-0.60	0.35
Leu	245	.	A	B	B	.	.	.	-0.26	*	.	.	-0.60	0.21
Thr	246	.	A	B	B	.	.	.	-1.11	*	.	.	-0.60	0.21
Leu	247	.	A	B	B	.	.	.	-1.70	*	.	.	-0.60	0.22
Met	248	A	A	.	B	.	.	.	-2.26	*	*	.	-0.60	0.27
Ser	249	A	A	.	B	.	.	.	-1.26	*	*	.	-0.60	0.19
Val	250	A	A	.	B	.	.	.	-1.33	*	*	.	-0.30	0.45
Ala	251	A	A	.	B	.	.	.	-1.27	*	*	.	-0.30	0.32
Ala	252	A	A	.	B	.	.	.	-0.41	*	*	.	-0.60	0.37
Arg	253	A	A	.	B	.	.	.	0.16	*	*	.	-0.15	1.01
Ile	254	A	A	.	B	.	.	.	0.24	*	*	.	0.45	1.36
Tyr	255	A	.	.	.	.	.	.	0.80	*	*	.	0.99	2.08
Lys	256	.	.	B	.	.	.	.	0.50	*	*	.	1.33	1.42
His	257	.	.	B	.	.	T	.	1.13	.	*	F	1.12	1.42
Pro	258	.	.	.	.	.	T	C	1.02	.	*	F	2.56	1.81
Ser	259	.	.	.	.	T	T	.	1.61	.	*	F	3.40	1.46
Ile	260	.	.	.	.	T	T	.	0.97	.	*	F	2.76	1.44
Lys	261	.	.	B	.	.	.	.	0.92	.	*	F	1.67	0.65
Asn	262	.	.	.	.	T	.	.	0.14	*	*	F	1.73	0.78

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ser	263	.	.	B	B	.	.	.	-0.24	*	*	F	0.19	0.92
Ile	264	.	.	B	B	.	.	.	-0.80	*	*	.	-0.30	0.45
Asn	265	.	.	B	B	.	.	.	-0.77	*	*	.	-0.60	0.21
Leu	266	.	.	B	B	.	.	.	-0.77	.	*	.	-0.60	0.12
Met	267	A	.	.	B	.	.	.	-1.62	*	.	.	-0.60	0.33
Val	268	.	.	B	B	.	.	.	-2.13	.	*	.	-0.60	0.15
Val	269	.	.	B	B	.	.	.	-2.13	.	.	.	-0.60	0.15
Lys	270	A	.	.	B	.	.	.	-2.99	.	.	.	-0.60	0.11
Val	271	.	.	B	B	.	.	.	-2.18	.	.	.	-0.60	0.11
Leu	272	.	.	B	B	.	.	.	-1.58	.	.	.	-0.30	0.25
Ile	273	A	.	.	B	.	.	.	-0.72	.	.	.	0.30	0.21
Val	274	A	.	.	B	.	.	.	0.18	.	*	.	0.30	0.49
Glu	275	A	.	.	B	.	.	.	-0.16	.	.	.	0.75	1.19
Asp	276	A	A	.	.	.	.	.	0.36	.	.	F	0.90	1.79
Glu	277	A	A	.	.	.	.	.	0.96	*	.	F	0.90	2.39
Lys	278	.	A	.	.	T	.	.	1.84	*	*	F	1.30	2.13
Trp	279	.	A	.	.	.	.	C	1.84	.	*	F	1.10	2.21
Gly	280	.	.	.	.	.	T	C	1.54	*	.	F	1.35	0.95
Pro	281	.	.	.	.	.	T	C	1.54	*	*	F	1.36	0.64
Glu	282	.	.	B	.	.	T	.	1.54	*	*	F	1.62	1.01
Val	283	.	.	B	.	.	T	.	1.16	*	*	F	2.23	1.64
Ser	284	.	.	.	.	.	T	C	1.10	.	*	F	2.74	1.05

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asp	285	.	.	.	.	T	T	.	0.63	.	.	F	3.10	0.60
Asn	286	.	.	.	.	T	T	.	0.53	.	*	F	2.49	0.67
Gly	287	.	.	.	.	T	T	.	-0.28	*	*	F	2.18	0.72
Gly	288	.	.	.	.	T	.	.	0.69	*	*	F	1.07	0.35
Leu	289	.	.	B	.	.	.	.	0.99	*	*	F	0.36	0.43
Thr	290	.	.	B	.	.	.	.	0.29	*	*	.	-0.10	0.70
Leu	291	.	.	B	.	.	.	.	-0.38	*	*	.	-0.40	0.61
Arg	292	.	.	B	.	.	.	.	-0.03	*	*	.	-0.40	0.40
Asn	293	.	.	B	.	.	.	.	0.02	*	*	.	-0.10	0.44
Phe	294	.	.	.	.	T	T	.	0.83	*	*	.	0.20	0.57
Cys	295	.	.	.	.	T	T	.	1.26	*	*	.	0.20	0.50
Asn	296	.	.	.	.	T	T	.	2.18	*	*	.	0.20	0.61
Trp	297	.	.	.	.	T	T	.	1.37	*	*	.	0.65	1.38
Gln	298	.	.	.	.	T	.	.	1.37	*	.	.	0.45	2.23
Arg	299	.	.	.	.	T	.	.	2.07	*	.	.	1.05	2.23
Arg	300	.	.	.	.	T	.	.	2.52	*	*	F	1.20	3.67
Phe	301	.	.	.	.	T	.	.	2.22	*	*	F	1.84	3.28
Asn	302	.	.	.	.	T	.	.	2.51	*	*	F	2.18	2.24
Gln	303	.	.	.	.	.	T	C	2.62	*	.	F	2.52	1.91
Pro	304	.	.	.	.	.	T	C	2.48	*	.	F	2.86	4.33
Ser	305	.	.	.	.	T	T	.	2.16	*	*	F	3.40	3.66
Asp	306	.	.	.	.	T	T	.	2.86	*	.	F	3.06	3.27

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Arg	307	.	.	.	.	.	.	C	2.82	*	.	F	2.32	3.66
His	308	.	.	.	.	.	.	C	2.58	*	.	F	1.98	3.72
Pro	309	.	.	.	.	.	.	C	2.79	*	.	F	1.64	3.49
Glu	310	.	.	.	.	T	.	.	2.78	*	.	F	1.50	2.97
His	311	A	.	.	.	.	T	.	2.19	*	.	F	1.00	3.15
Tyr	312	A	.	.	.	.	T	.	1.19	*	.	F	1.00	2.06
Asp	313	A	.	.	.	.	T	.	0.41	.	.	F	0.85	0.83
Thr	314	A	.	.	.	.	T	.	-0.19	.	.	.	-0.20	0.51
Ala	315	A	.	.	B	.	.	.	-0.50	*	.	.	-0.60	0.27
Ile	316	.	.	B	B	.	.	.	-0.36	*	.	.	-0.60	0.23
Leu	317	.	.	B	B	.	.	.	-0.11	.	.	.	-0.60	0.31
Leu	318	.	.	B	B	.	.	.	-0.11	.	*	.	-0.60	0.53
Thr	319	.	.	B	B	.	.	.	-0.50	.	.	F	0.00	1.23
Arg	320	.	.	B	B	.	.	.	-0.58	.	*	F	-0.08	1.29
Gln	321	.	.	.	B	T	.	.	-0.03	.	*	F	0.69	0.84
Asn	322	.	.	.	.	T	T	.	0.78	.	*	F	1.31	0.57
Phe	323	.	.	.	.	T	T	.	1.59	.	.	.	1.98	0.51
Cys	324	.	.	.	.	T	T	.	1.56	.	*	.	2.20	0.51
Gly	325	.	.	.	.	T	T	.	0.63	.	*	F	1.53	0.31
Gln	326	.	.	.	.	T	.	.	-0.03	.	.	F	1.11	0.30
Glu	327	.	.	.	.	T	.	.	-0.03	.	.	F	0.89	0.30
Gly	328	.	.	.	.	T	.	.	0.36	.	.	F	1.27	0.50

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	329	.	.	B	.	.	.	.	0.21	.	.	F	0.65	0.42
Cys	330	.	.	B	.	.	.	.	0.21	.	.	.	0.50	0.20
Asp	331	.	.	B	.	.	T	.	-0.64	.	.	.	0.10	0.20
Thr	332	.	.	B	.	.	T	.	-1.23	*	.	.	-0.20	0.18
Leu	333	.	.	B	.	.	T	.	-0.89	.	.	.	0.10	0.34
Gly	334	.	.	B	.	.	T	.	-0.97	.	.	.	0.70	0.34
Val	335	.	.	B	.	.	.	.	-0.64	.	.	.	-0.40	0.16
Ala	336	.	.	B	.	.	.	.	-0.96	.	.	.	-0.10	0.20
Asp	337	.	.	B	.	.	T	.	-1.53	.	.	.	0.10	0.29
Ile	338	.	.	B	.	.	T	.	-1.39	.	.	.	-0.20	0.27
Gly	339	.	.	B	.	.	T	.	-1.04	*	.	.	0.10	0.14
Thr	340	.	.	B	.	.	T	.	-0.40	.	.	.	0.70	0.14
Ile	341	.	.	B	.	.	.	.	0.19	.	.	.	0.24	0.32
Cys	342	.	.	B	.	.	.	.	0.23	.	.	.	1.18	0.52
Asp	343	.	.	B	.	.	T	.	0.82	*	.	F	1.87	0.72
Pro	344	.	.	.	.	T	T	.	0.50	.	.	F	3.06	1.37
Asn	345	.	.	.	.	T	T	.	0.51	.	.	F	3.40	1.37
Lys	346	.	.	.	.	T	T	.	0.54	*	.	F	3.06	1.10
Ser	347	.	.	.	B	T	.	.	0.32	.	.	F	1.87	0.53
Cys	348	.	.	B	B	.	.	.	0.32	*	.	.	0.38	0.23
Ser	349	.	.	B	B	.	.	.	0.53	*	.	.	0.64	0.20
Val	350	.	.	B	B	.	.	.	0.53	*	.	.	0.30	0.25

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ile	351	.	.	B	B	.	.	.	0.14	*	.	.	0.60	0.80
Glu	352	A	.	.	B	.	.	.	-0.37	.	.	.	0.60	0.59
Asp	353	A	A	.	.	.	.	.	0.30	.	.	F	0.75	0.66
Glu	354	A	A	.	.	.	.	.	0.01	*	.	F	0.90	1.62
Gly	355	A	A	.	.	.	.	.	0.28	*	.	F	0.75	0.95
Leu	356	A	A	.	.	.	.	.	1.13	*	.	.	0.30	0.57
Gln	357	A	A	.	.	.	.	.	0.82	*	.	.	-0.30	0.45
Ala	358	A	A	.	.	.	.	.	0.01	*	.	.	-0.60	0.66
Ala	359	A	A	.	.	.	.	.	-0.58	*	.	.	-0.60	0.66
His	360	A	A	.	.	.	.	.	-0.27	*	.	.	-0.60	0.38
Thr	361	A	A	.	.	.	.	.	0.54	*	.	.	-0.60	0.52
Leu	362	A	A	.	.	.	.	.	-0.27	*	.	.	-0.30	0.88
Ala	363	A	A	.	.	.	.	.	-0.02	*	.	.	-0.30	0.54
His	364	A	A	.	.	.	.	.	0.53	*	.	.	-0.30	0.37
Glu	365	A	A	.	.	.	.	.	-0.29	*	.	.	-0.30	0.61
Leu	366	A	A	.	B	.	.	.	-0.79	*	.	.	-0.30	0.45
Gly	367	A	A	.	B	.	.	.	-0.28	*	.	.	-0.60	0.27
His	368	A	A	.	B	.	.	.	-0.29	*	.	.	-0.30	0.21
Val	369	A	A	.	B	.	.	.	-0.47	*	.	.	-0.60	0.25
Leu	370	.	A	B	B	.	.	.	-0.50	*	.	.	-0.26	0.39
Ser	371	.	A	B	B	.	.	.	0.31	*	.	.	0.08	0.39
Met	372	.	.	B	.	.	.	.	0.66	.	.	.	0.92	0.88

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Pro	373	.	.	.	.	T	.	.	0.39	*	.	.	2.41	1.78
His	374	.	.	.	.	T	T	.	1.29	*	.	F	3.40	1.78
Asp	375	.	.	.	.	T	T	.	1.89	.	.	F	3.06	3.61
Asp	376	.	.	.	.	T	T	.	1.52	.	.	F	2.89	3.61
Ser	377	.	.	.	.	T	T	.	1.81	*	*	F	2.72	1.42
Lys	378	.	.	B	.	.	T	.	2.13	*	*	F	2.15	1.23
Pro	379	.	.	.	.	T	T	.	1.36	*	*	F	2.38	1.44
Cys	380	.	.	B	.	.	T	.	0.66	*	*	F	1.70	0.89
Thr	381	.	.	B	.	.	T	.	0.31	*	*	F	1.53	0.38
Arg	382	.	.	B	B	.	.	.	0.40	*	*	F	0.36	0.25
Leu	383	.	.	B	B	.	.	.	-0.24	*	*	.	0.04	0.71
Phe	384	.	.	B	B	.	.	.	-0.38	*	.	.	-0.43	0.49
Gly	385	.	.	.	B	.	.	C	0.33	*	.	F	0.05	0.25
Pro	386	.	.	.	.	.	T	C	0.61	*	*	F	0.45	0.59
Met	387	.	.	.	.	T	T	.	0.47	*	*	F	0.65	0.93
Gly	388	A	.	.	.	.	T	.	0.42	.	.	F	1.00	1.29
Lys	389	A	.	.	.	.	T	.	0.52	.	.	.	0.10	0.62
His	390	A	A	.	.	.	.	.	0.28	.	.	.	-0.30	0.62
His	391	A	A	.	.	.	.	.	0.28	.	*	.	-0.30	0.63
Val	392	.	A	B	.	.	.	.	0.07	.	.	.	-0.30	0.49
Met	393	A	A	.	.	.	.	.	-0.29	.	*	.	-0.60	0.30
Ala	394	A	A	.	.	.	.	.	-1.19	.	*	.	-0.60	0.19

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Pro	395	A	A	.	.	.	.	.	-1.19	.	*	.	-0.60	0.19
Leu	396	A	A	.	.	.	.	.	-1.97	.	*	.	-0.60	0.26
Phe	397	A	A	.	.	.	.	.	-1.11	*	*	.	-0.60	0.21
Val	398	A	A	.	.	.	.	.	-0.51	*	.	.	-0.60	0.22
His	399	.	A	B	.	.	.	.	-0.23	*	*	.	-0.60	0.46
Leu	400	.	A	B	.	.	.	.	-0.83	*	*	.	-0.60	0.77
Asn	401	.	A	.	.	T	.	.	-0.23	*	*	F	-0.05	0.85
Gln	402	.	A	.	.	T	.	.	0.18	.	*	F	-0.05	0.97
Thr	403	.	A	.	.	T	.	.	0.73	.	*	F	0.10	1.24
Leu	404	.	A	.	.	.	.	C	0.56	.	*	F	-0.10	1.03
Pro	405	.	.	.	.	T	.	.	0.70	.	.	.	0.00	0.92
Trp	406	.	.	.	.	T	.	.	0.40	.	.	.	0.00	0.34
Ser	407	.	.	.	.	.	T	C	-0.19	.	.	.	0.00	0.55
Pro	408	.	.	.	.	T	T	.	-0.48	.	.	.	0.20	0.36
Cys	409	.	.	.	.	T	T	.	0.09	.	.	.	0.20	0.34
Ser	410	.	.	B	.	.	T	.	-0.51	.	.	.	-0.20	0.40
Ala	411	.	A	B	.	.	.	.	-0.53	.	.	.	-0.60	0.21
Met	412	.	A	B	.	.	.	.	-0.23	.	.	.	-0.60	0.57
Tyr	413	.	A	B	.	.	.	.	-0.83	.	.	.	-0.60	0.74
Leu	414	.	A	B	.	.	.	.	-0.98	*	.	.	-0.60	0.60
Thr	415	.	A	B	.	.	.	.	-0.68	*	.	.	-0.60	0.50
Glu	416	A	A	.	.	.	.	.	-0.43	*	.	.	-0.30	0.54

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	417	A	A	.	.	.	.	.	-0.18	*	.	F	0.76	0.64
Leu	418	A	.	.	.	.	T	.	0.03	*	.	F	1.47	0.44
Asp	419	.	.	.	.	T	T	.	0.50	*	.	F	2.18	0.35
Gly	420	.	.	.	.	T	T	.	0.81	.	.	F	1.89	0.42
Gly	421	.	.	.	.	T	T	.	0.14	.	.	F	3.10	0.84
His	422	.	.	.	.	T	T	.	0.14	.	.	F	2.79	0.27
Gly	423	.	.	.	.	T	T	.	0.14	.	.	F	1.58	0.23
Asp	424	.	.	B	.	.	T	.	0.14	.	*	.	0.72	0.19
Cys	425	.	.	B	.	.	T	.	-0.10	.	*	.	1.01	0.23
Leu	426	.	.	B	.	.	.	.	0.03	.	*	.	0.50	0.24
Leu	427	.	.	B	.	.	.	.	-0.28	.	*	.	0.50	0.22
Asp	428	.	.	B	.	.	.	.	-0.52	*	*	.	-0.10	0.40
Ala	429	.	.	B	.	.	T	.	-1.11	*	.	F	0.25	0.49
Pro	430	A	.	.	.	.	T	.	-1.26	.	.	F	0.25	0.60
Gly	431	.	.	.	.	T	T	.	-0.66	.	.	F	0.65	0.30
Ala	432	.	.	B	.	.	T	.	-0.66	.	.	.	-0.20	0.46
Ala	433	.	.	B	.	.	.	.	-0.87	.	.	.	-0.40	0.24
Leu	434	.	.	B	.	.	.	.	-0.59	.	.	.	-0.40	0.38
Pro	435	.	.	B	.	.	.	.	-0.72	.	.	.	-0.40	0.54
Leu	436	.	.	B	.	.	T	.	-1.19	.	.	.	-0.20	0.53
Pro	437	.	.	B	.	.	T	.	-0.81	.	.	F	0.00	0.53
Thr	438	.	.	.	.	T	T	.	-0.57	.	*	F	0.45	0.53

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	439	.	.	.	.	.	T	C	0.36	.	*	F	0.30	0.64
Leu	440	.	.	.	.	.	T	C	-0.03	.	*	F	1.25	0.81
Pro	441	.	.	B	.	.	T	.	0.19	.	*	F	0.50	0.55
Gly	442	.	.	B	.	.	T	.	-0.41	.	*	F	0.45	0.57
Arg	443	.	.	B	.	.	T	.	-0.34	.	*	.	0.25	0.57
Met	444	.	A	B	.	.	.	.	0.00	.	*	.	-0.50	0.57
Ala	445	.	A	B	.	.	.	.	0.00	*	*	.	-0.10	1.00
Leu	446	.	A	B	.	.	.	.	0.21	*	.	.	-0.60	0.42
Tyr	447	.	A	B	.	.	.	.	0.56	*	*	.	-0.60	0.71
Gln	448	.	A	B	.	.	.	.	0.44	*	*	.	-0.45	1.22
Leu	449	A	A	.	.	.	.	.	0.38	*	*	.	-0.15	2.57
Asp	450	A	A	.	.	.	.	.	1.08	*	*	F	-0.15	0.88
Gln	451	.	A	B	.	.	.	.	1.89	*	*	F	0.75	0.99
Gln	452	.	A	B	.	.	.	.	1.24	*	*	F	0.90	2.09
Cys	453	.	A	B	.	.	.	.	0.54	*	*	F	0.75	0.88
Arg	454	.	A	B	.	.	.	.	1.01	*	*	.	-0.30	0.44
Gln	455	.	A	B	.	.	.	.	0.80	*	*	.	-0.30	0.25
Ile	456	.	A	B	.	.	.	.	0.80	*	.	.	-0.30	0.72
Phe	457	.	A	.	.	T	.	.	0.10	*	*	.	0.70	0.62
Gly	458	.	.	.	.	.	T	C	0.88	*	*	.	0.00	0.31
Pro	459	.	.	.	.	T	T	.	0.73	*	*	F	0.65	0.86
Asp	460	.	.	.	.	T	T	.	0.07	*	*	F	1.40	1.35

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Phe	461	.	.	.	.	T	T	.	0.74	*	*	.	1.35	0.73
Arg	462	.	.	.	.	T	.	.	1.44	*	*	.	1.40	0.73
His	463	.	.	.	.	T	.	.	1.48	*	*	.	1.65	0.71
Cys	464	.	.	.	.	.	T	C	1.39	*	*	.	1.45	1.18
Pro	465	.	.	.	.	T	T	.	0.80	*	.	F	2.50	0.80
Asn	466	.	.	.	.	T	T	.	1.50	*	*	F	1.65	0.60
Thr	467	.	.	.	.	T	T	.	1.39	*	*	F	1.55	1.93
Ser	468	.	A	.	.	T	.	.	0.57	*	.	F	1.50	2.08
Ala	469	.	A	.	.	T	.	.	0.57	.	.	F	1.10	0.96
Gln	470	.	A	B	.	.	.	.	0.19	.	.	F	0.45	0.36
Asp	471	.	A	B	.	.	.	.	0.19	*	*	F	0.45	0.27
Val	472	.	A	B	.	.	.	.	-0.31	*	.	.	-0.30	0.46
Cys	473	.	A	B	.	.	.	.	-0.30	*	.	.	-0.30	0.22
Ala	474	.	A	B	.	.	.	.	-0.38	*	*	.	-0.60	0.14
Gln	475	.	A	B	.	.	.	.	-0.41	.	*	.	-0.60	0.10
Leu	476	.	A	B	.	.	.	.	-0.72	*	*	.	-0.60	0.25
Trp	477	.	A	B	.	.	.	.	0.13	.	*	.	-0.60	0.36
Cys	478	.	A	B	.	.	.	.	0.46	.	.	.	-0.26	0.35
His	479	.	.	.	.	T	T	.	0.46	.	.	.	0.88	0.42
Thr	480	.	.	.	.	T	T	.	0.46	.	*	.	1.52	0.40
Asp	481	.	.	.	.	T	T	.	1.06	.	.	F	3.06	1.30
Gly	482	.	.	.	.	T	T	.	0.53	.	.	F	3.40	1.48

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ala	483	.	.	.	.	T	.	C	0.53	*	.	F	2.41	0.85
Glu	484	A	.	.	.	.	.	.	0.53	*	.	F	1.67	0.27
Pro	485	A	.	.	.	.	.	.	0.53	.	.	F	0.73	0.37
Leu	486	A	.	.	.	.	.	.	0.58	*	.	.	0.24	0.53
Cys	487	A	.	.	.	.	.	.	0.92	.	.	.	0.78	0.62
His	488	.	.	B	.	.	.	.	1.17	.	.	F	0.61	0.64
Thr	489	.	.	.	.	T	T	.	0.87	.	.	F	1.49	0.77
Lys	490	.	.	.	.	T	T	.	0.27	.	.	F	2.52	1.92
Asn	491	.	.	.	.	T	T	.	0.87	.	.	F	2.80	1.16
Gly	492	.	.	.	.	T	T	.	1.24	.	.	F	2.52	1.25
Ser	493	.	.	.	.	.	.	C	0.69	.	.	F	1.09	0.66
Leu	494	.	.	.	.	.	.	C	1.00	.	.	.	0.36	0.41
Pro	495	.	.	B	.	.	.	.	0.61	.	.	.	0.18	0.69
Trp	496	.	.	.	.	T	T	.	0.30	.	.	.	0.50	0.51
Ala	497	.	.	B	.	.	T	.	0.43	.	.	.	0.05	0.90
Asp	498	.	.	.	.	T	T	.	0.07	.	.	F	1.15	0.90
Gly	499	.	.	.	.	T	T	.	0.53	.	.	F	1.40	0.46
Thr	500	.	.	.	.	.	T	C	0.53	.	.	F	2.05	0.45
Pro	501	.	.	.	.	T	T	.	0.48	.	.	F	2.50	0.42
Cys	502	.	.	.	.	T	T	.	1.03	.	*	F	1.65	0.42
Gly	503	.	.	.	.	.	T	C	0.22	.	.	F	1.20	0.39
Pro	504	.	.	.	.	T	.	.	-0.10	.	.	F	0.65	0.21

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gly	505	.	.	.	.	T	.	.	-0.09	.	.	.	0.25	0.21
His	506	.	.	B	.	.	.	.	0.12	.	.	.	-0.40	0.28
Leu	507	.	.	B	.	.	.	.	0.44	.	.	.	0.50	0.32
Cys	508	.	.	B	.	.	T	.	0.49	.	*	.	0.91	0.32
Ser	509	.	.	.	.	T	T	.	0.03	.	.	F	1.67	0.31
Glu	510	.	.	.	.	T	T	.	-0.43	.	.	F	1.28	0.20
Gly	511	.	.	.	.	T	T	.	-0.61	*	.	F	1.49	0.31
Ser	512	.	.	.	.	T	.	.	0.20	*	.	F	2.10	0.36
Cys	513	.	A	.	.	.	.	C	0.87	.	.	F	1.79	0.36
Leu	514	.	A	.	.	.	.	C	1.17	.	.	F	1.58	0.63
Pro	515	A	A	.	.	.	.	.	0.31	.	.	F	1.17	0.81
Glu	516	A	A	.	.	.	.	.	0.66	*	.	F	1.11	1.13
Glu	517	A	A	.	.	.	.	.	1.07	*	.	F	0.90	2.37
Glu	518	A	A	.	.	.	.	.	1.52	.	.	F	0.90	3.00
Val	519	A	A	.	.	.	.	.	2.38	.	.	F	0.90	2.68
Glu	520	A	A	.	.	.	.	.	2.38	*	.	F	0.90	3.09
Arg	521	A	.	.	.	.	T	.	1.52	*	.	F	1.30	2.76
Pro	522	A	.	.	.	.	T	.	0.67	*	*	F	1.30	2.76
Lys	523	A	.	.	.	.	T	.	0.67	*	*	F	1.30	1.18
Pro	524	.	.	B	.	.	T	.	1.18	*	*	F	1.30	1.01
Val	525	.	.	B	.	.	.	.	0.83	*	*	F	0.65	0.65
Val	526	.	.	B	.	.	.	.	0.43	.	*	F	0.65	0.32

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asp	527	.	.	B	.	.	T	.	0.06	*	.	F	-0.05	0.22
Gly	528	.	.	B	.	.	T	.	-0.20	*	.	F	-0.05	0.30
Gly	529	.	.	.	.	T	T	.	-0.28	.	.	F	0.65	0.62
Trp	530	.	.	.	.	.	T	C	0.23	.	.	.	0.00	0.39
Ala	531	.	.	.	.	.	.	C	0.88	.	.	.	-0.20	0.39
Pro	532	.	.	.	.	T	.	.	0.59	.	.	.	0.00	0.61
Trp	533	.	.	.	.	T	.	.	0.59	.	.	.	0.00	0.61
Gly	534	.	.	.	.	.	T	C	0.93	.	.	.	0.00	0.59
Pro	535	.	.	.	.	T	T	.	0.56	.	.	F	0.35	0.66
Trp	536	.	.	.	.	T	T	.	0.84	*	.	F	0.66	0.34
Gly	537	.	.	.	.	.	T	C	1.17	*	.	F	1.07	0.46
Glu	538	.	.	.	.	T	.	.	1.14	*	.	F	1.98	0.58
Cys	539	.	.	.	.	T	T	.	0.82	*	.	F	2.49	0.80
Ser	540	.	.	.	.	T	T	.	0.69	*	.	F	3.10	0.43
Arg	541	.	.	.	.	T	T	.	0.63	*	.	F	2.79	0.25
Thr	542	.	.	.	.	T	T	.	0.63	*	.	F	2.18	0.46
Cys	543	.	.	.	.	T	T	.	-0.22	*	.	F	1.87	0.34
Gly	544	.	.	.	.	T	T	.	0.44	*	.	F	1.56	0.13
Gly	545	.	.	.	.	T	T	.	0.04	*	*	F	0.65	0.15
Gly	546	.	.	.	.	T	T	.	-0.37	*	*	F	0.35	0.25
Val	547	.	.	B	B	.	.	.	-0.09	*	*	.	-0.60	0.33
Gln	548	.	.	B	B	.	.	.	0.69	*	*	.	-0.60	0.46

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Phe	549	.	.	B	B	.	.	.	1.03	*	*	.	-0.30	0.91
Ser	550	.	.	B	B	.	.	.	0.71	*	*	.	0.79	2.13
His	551	.	.	B	.	.	.	.	1.10	*	*	.	1.18	0.66
Arg	552	.	.	.	.	T	.	.	1.96	*	*	.	2.37	1.52
Glu	553	.	.	.	.	T	.	.	1.74	*	*	F	2.86	1.89
Cys	554	.	.	.	.	T	T	.	2.44	*	.	F	3.40	2.15
Lys	555	.	.	.	.	T	T	.	2.53	*	.	F	3.06	1.90
Asp	556	.	.	.	.	.	T	C	2.57	*	.	F	2.52	1.70
Pro	557	.	.	.	.	.	T	C	2.46	*	.	F	2.52	5.49
Glu	558	.	.	.	.	.	.	C	2.11	.	.	F	2.32	4.41
Pro	559	.	.	.	.	T	T	.	2.43	.	*	F	2.72	2.62
Gln	560	.	.	.	.	T	T	.	2.50	.	*	F	2.76	1.67
Asn	561	.	.	.	.	T	T	.	2.26	*	*	F	3.40	1.89
Gly	562	.	.	.	.	T	T	.	1.80	*	*	F	2.76	1.92
Gly	563	.	.	.	.	T	T	.	0.99	*	*	F	2.27	0.59
Arg	564	.	.	B	.	.	T	.	0.86	*	.	F	0.93	0.30
Tyr	565	.	.	B	.	.	T	.	0.97	.	.	.	0.44	0.30
Cys	566	.	.	B	.	.	T	.	1.08	.	.	.	1.00	0.60
Leu	567	.	.	B	.	.	.	.	0.83	.	*	.	1.40	0.60
Gly	568	.	.	B	.	.	.	.	1.22	.	*	F	1.55	0.39
Arg	569	.	.	B	.	.	.	.	0.87	.	*	F	2.30	1.45
Arg	570	.	.	.	.	T	.	.	1.11	*	*	F	3.00	2.75

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ala	571	.	.	.	.	T	.	.	1.48	*	*	F	2.70	4.82
Lys	572	.	.	.	.	T	.	.	1.62	*	*	F	2.40	3.30
Tyr	573	.	.	.	.	T	T	.	1.93	*	.	F	1.85	0.90
Gln	574	.	.	.	.	T	T	.	1.51	.	.	F	1.10	1.22
Ser	575	.	.	.	.	T	T	.	1.40	.	*	.	0.50	0.88
Cys	576	.	.	.	.	T	T	.	1.99	.	.	.	0.50	0.97
His	577	.	A	B	.	.	.	.	1.28	.	.	.	0.60	0.97
Thr	578	.	A	.	.	T	.	.	1.31	.	.	F	0.85	0.39
Glu	579	.	A	.	.	T	.	.	1.10	.	.	F	1.00	1.12
Glu	580	.	A	.	.	T	.	.	1.40	.	.	F	1.64	1.27
Cys	581	.	A	B	.	.	.	.	1.72	.	*	F	1.58	1.47
Pro	582	.	.	.	.	.	T	C	1.80	.	*	F	2.37	0.84
Pro	583	.	.	.	.	T	T	.	1.81	*	.	F	2.91	0.97
Asp	584	.	.	.	.	T	T	.	1.11	*	.	F	3.40	2.43
Gly	585	.	.	.	.	T	T	.	1.22	*	.	F	3.06	1.36
Lys	586	.	A	.	.	T	.	.	1.89	*	.	F	2.32	1.72
Ser	587	A	A	.	.	.	.	.	2.10	.	.	F	1.58	1.79
Phe	588	A	A	.	.	.	.	.	2.31	.	.	F	1.24	3.13
Arg	589	A	A	.	.	.	.	.	1.64	.	.	F	0.90	2.71
Glu	590	A	A	.	.	.	.	.	1.99	.	.	F	0.60	1.08
Gln	591	A	A	.	.	.	.	.	1.99	.	.	F	0.90	2.17
Gln	592	A	A	.	.	.	.	.	2.04	.	*	F	0.90	2.21

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Cys	593	A	A	.	.	.	.	.	2.74	.	*	F	1.15	2.00
Glu	594	.	A	.	.	T	.	.	2.04	.	.	F	1.50	1.86
Lys	595	.	A	.	.	T	.	.	1.80	.	.	F	1.75	1.08
Tyr	596	.	.	.	.	T	.	.	1.80	.	.	.	2.05	3.17
Asn	597	.	.	.	.	T	T	.	1.56	.	.	.	2.50	2.94
Ala	598	.	.	.	.	T	T	.	1.91	.	.	.	1.35	2.30
Tyr	599	.	.	B	.	.	T	.	1.91	.	.	.	0.70	2.12
Asn	600	.	.	B	.	.	T	.	1.27	.	*	.	0.75	2.20
Tyr	601	.	.	B	.	.	.	.	1.51	.	.	.	0.25	2.16
Thr	602	.	.	B	.	.	.	.	1.17	.	*	F	0.70	2.30
Asp	603	.	.	B	.	.	T	.	1.76	.	*	F	1.75	1.42
Met	604	.	.	B	.	.	T	.	1.19	.	*	F	2.00	1.45
Asp	605	.	.	.	.	T	T	.	0.38	*	.	F	2.50	0.83
Gly	606	.	.	B	.	.	T	.	0.62	*	*	F	1.85	0.41
Asn	607	.	.	B	B	.	.	.	0.64	*	*	F	0.60	0.72
Leu	608	A	.	.	B	.	.	.	-0.21	*	*	.	-0.10	0.45
Leu	609	.	.	B	B	.	.	.	0.18	*	*	.	-0.35	0.34
Gln	610	.	.	B	B	.	.	.	0.22	*	.	.	-0.60	0.33
Trp	611	.	.	B	B	.	.	.	0.32	*	.	.	-0.60	0.79
Val	612	.	.	B	B	.	.	.	-0.27	*	.	.	-0.45	1.50
Pro	613	.	.	B	.	.	T	.	0.20	*	.	.	-0.20	0.88

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Lys	614	.	.	B	.	.	T	.	0.16	*	*	.	-0.20	0.82
Tyr	615	.	.	B	.	.	T	.	-0.14	.	.	.	0.10	0.82
Ala	616	.	.	.	.	T	T	.	-0.07	*	*	.	0.50	0.71
Gly	617	.	.	.	.	T	.	.	0.90	*	.	.	0.64	0.55
Val	618	.	.	B	.	.	.	.	1.11	.	*	.	0.58	0.69
Ser	619	.	.	B	.	.	T	.	1.18	.	*	F	2.32	1.14
Pro	620	.	.	B	.	.	T	.	0.76	.	*	F	2.66	2.26
Arg	621	.	.	.	.	T	T	.	1.39	.	*	F	3.40	1.63
Asp	622	.	.	.	.	T	T	.	0.92	.	*	F	3.06	2.43
Arg	623	.	A	.	.	T	.	.	1.08	.	*	F	2.32	1.30
Cys	624	.	A	B	.	.	.	.	0.71	*	*	F	1.43	0.57
Lys	625	.	A	B	.	.	.	.	1.03	*	*	.	0.64	0.18
Leu	626	.	A	B	.	.	.	.	0.33	*	*	.	0.30	0.18
Phe	627	.	A	B	.	.	.	.	0.44	.	*	.	0.04	0.35
Cys	628	.	A	B	.	.	.	.	-0.01	.	*	.	0.98	0.34
Arg	629	.	A	B	.	.	.	.	0.77	*	*	.	1.32	0.41
Ala	630	A	.	.	.	.	T	.	0.42	*	*	.	2.36	0.92
Arg	631	.	.	.	.	T	T	.	1.23	.	*	F	3.40	2.31
Gly	632	.	.	.	.	T	T	.	1.23	.	*	F	3.06	2.04
Arg	633	.	.	.	.	T	T	.	1.94	.	*	F	2.72	1.75
Ser	634	A	A	.	.	.	.	.	0.98	*	*	F	1.58	1.79

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Glu	635	A	A	.	.	.	.	.	0.87	*	*	F	1.24	1.34
Phe	636	A	A	.	.	.	.	.	0.76	*	*	F	0.45	0.59
Lys	637	A	A	.	.	.	.	.	0.51	*	*	.	0.30	0.77
Val	638	A	A	.	.	.	.	.	0.44	*	*	.	0.30	0.45
Phe	639	A	A	.	.	.	.	.	-0.11	.	.	.	0.45	1.03
Glu	640	A	A	.	.	.	.	.	-1.00	*	.	.	0.30	0.38
Ala	641	A	.	.	B	.	.	.	-0.30	*	.	.	-0.30	0.36
Lys	642	A	.	.	B	.	.	.	-0.69	.	.	.	0.30	0.70
Val	643	A	.	.	B	.	.	.	-0.14	.	.	.	0.60	0.40
Ile	644	A	.	.	B	.	.	.	-0.26	.	*	F	0.45	0.57
Asp	645	.	.	B	B	.	.	.	-0.92	.	.	F	0.45	0.23
Gly	646	.	.	B	B	.	.	.	-0.68	*	.	F	-0.45	0.17
Thr	647	.	.	B	B	.	.	.	-0.93	*	.	F	-0.15	0.24
Leu	648	.	.	.	B	.	.	C	-0.08	.	.	F	0.05	0.22
Cys	649	.	.	.	B	T	.	.	0.50	*	*	.	0.10	0.39
Gly	650	.	.	.	.	.	T	C	-0.31	.	.	F	0.45	0.39
Pro	651	.	.	.	.	T	T	.	-0.56	.	.	F	0.65	0.39
Glu	652	A	.	.	.	.	T	.	-1.13	.	.	F	0.25	0.73
Thr	653	A	.	.	.	.	T	.	-0.99	.	.	F	0.25	0.52
Leu	654	A	.	.	B	.	.	.	-1.18	*	*	.	-0.30	0.18
Ala	655	.	.	B	B	.	.	.	-0.72	*	*	.	-0.60	0.08
Ile	656	.	.	B	B	.	.	.	-0.86	.	*	.	-0.60	0.10

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Cys	657	.	.	B	B	.	.	.	-0.86	.	*	.	-0.60	0.13
Val	658	A	.	.	B	.	.	.	-1.21	.	*	.	-0.30	0.21
Arg	659	.	.	B	B	.	.	.	-1.26	.	*	.	-0.30	0.16
Gly	660	.	.	.	B	T	T	.	-0.62	.	*	F	0.25	0.23
Gln	661	.	.	B	B	.	.	.	-0.32	.	*	F	0.45	0.61
Cys	662	.	.	B	B	.	.	.	0.00	.	*	.	0.30	0.32
Val	663	.	.	B	B	.	.	.	0.19	.	*	.	0.30	0.32
Lys	664	.	.	B	.	.	T	.	0.08	.	*	.	0.10	0.10
Ala	665	.	.	B	.	.	T	.	0.39	*	.	.	0.70	0.30
Gly	666	.	.	B	.	.	T	.	-0.47	*	.	.	0.70	0.56
Cys	667	.	.	B	.	.	T	.	-0.66	*	*	.	0.70	0.21
Asp	668	.	.	B	B	.	.	.	0.20	*	*	.	-0.30	0.15
His	669	.	.	B	B	.	.	.	-0.14	*	.	.	0.30	0.26
Val	670	.	.	B	B	.	.	.	0.23	*	.	.	0.30	0.64
Val	671	.	.	B	B	.	.	.	0.69	*	.	.	0.64	0.59
Asp	672	.	.	B	B	.	.	.	1.40	*	.	F	1.13	0.86
Ser	673	.	.	B	.	.	T	.	0.59	*	.	F	2.32	2.31
Pro	674	A	.	.	.	.	T	.	0.62	*	.	F	2.66	2.56
Arg	675	.	.	.	.	T	T	.	1.52	*	.	F	3.40	2.56
Lys	676	.	.	.	.	T	T	.	1.71	*	.	F	3.06	3.82
Leu	677	.	.	.	.	T	.	.	1.37	*	.	F	2.52	1.33
Asp	678	.	.	.	.	T	T	.	0.81	*	.	F	2.23	0.67

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Lys	679	.	.	B	.	.	T	.	0.36	*	.	F	1.49	0.25
Cys	680	.	.	B	.	.	T	.	-0.10	*	.	.	0.70	0.16
Gly	681	.	.	B	.	.	T	.	-0.49	*	.	.	0.70	0.10
Val	682	.	.	B	.	.	.	.	0.37	*	.	.	-0.10	0.05
Cys	683	.	.	B	.	.	T	.	0.02	.	.	.	0.10	0.18
Gly	684	.	.	.	.	T	T	.	-0.02	.	.	F	1.59	0.18
Gly	685	.	.	.	.	T	T	.	0.34	.	.	F	1.93	0.38
Lys	686	.	.	.	.	T	T	.	0.02	.	.	F	2.27	0.96
Gly	687	.	.	.	.	T	.	.	0.99	.	.	F	2.41	0.52
Asn	688	.	.	.	.	T	T	.	1.70	.	.	F	3.40	1.03
Ser	689	.	.	B	.	.	T	.	1.19	.	.	F	2.66	1.03
Cys	690	.	.	B	.	.	T	.	1.23	.	.	F	2.34	0.77
Arg	691	.	.	B	.	.	T	.	0.84	.	.	F	2.17	0.64
Lys	692	.	.	B	.	.	.	.	0.89	*	.	F	1.80	0.47
Val	693	.	.	B	.	.	T	.	0.08	*	.	F	1.98	1.18
Ser	694	.	.	B	.	.	T	.	0.07	*	.	F	1.70	0.50
Gly	695	.	.	B	.	.	T	.	0.52	*	.	F	0.93	0.36
Ser	696	.	.	B	.	.	T	.	0.10	*	.	F	0.46	0.75
Leu	697	.	.	B	.	.	.	.	0.06	.	*	F	0.39	0.81
Thr	698	.	.	B	.	.	.	.	0.67	.	.	F	0.37	1.31
Pro	699	.	.	B	.	.	T	.	0.62	.	.	F	0.10	1.53
Thr	700	.	.	.	.	T	T	.	0.72	.	.	F	0.50	1.84

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Asn	701	.	.	B	.	.	T	.	1.02	.	.	F	0.10	2.00
Tyr	702	.	.	.	.	T	T	.	1.83	*	.	.	0.35	2.08
Gly	703	.	.	.	.	T	T	.	1.26	*	.	.	0.65	2.41
Tyr	704	.	.	.	.	T	T	.	0.61	*	.	.	0.35	1.05
Asn	705	.	.	B	.	.	T	.	0.61	*	.	.	-0.20	0.50
Asp	706	.	.	B	.	.	T	.	-0.28	*	.	.	0.10	0.72
Ile	707	.	.	B	B	.	.	.	-0.24	*	.	.	-0.60	0.32
Val	708	.	.	B	B	.	.	.	-0.49	.	.	.	-0.30	0.31
Thr	709	.	.	B	B	.	.	.	-0.59	*	.	.	-0.60	0.19
Ile	710	.	.	B	B	.	.	.	-1.18	.	.	.	-0.60	0.27
Pro	711	.	.	B	.	.	T	.	-1.49	*	.	.	-0.20	0.36
Ala	712	.	.	B	.	.	T	.	-0.60	*	.	.	-0.20	0.36
Gly	713	.	.	.	.	.	T	C	-0.63	.	*	.	0.00	0.83
Ala	714	.	.	.	.	.	T	C	-0.32	.	*	F	0.15	0.38
Thr	715	.	.	B	B	.	.	.	-0.29	.	*	F	0.45	0.62
Asn	716	.	.	B	B	.	.	.	-0.03	.	*	F	-0.15	0.47
Ile	717	.	.	B	B	.	.	.	0.56	.	*	F	0.45	0.92
Asp	718	.	.	B	B	.	.	.	1.01	.	*	F	0.60	1.11
Val	719	.	.	B	B	.	.	.	1.30	.	*	F	0.90	1.35
Lys	720	.	.	B	B	.	.	.	1.58	.	*	F	0.90	2.58
Gln	721	.	.	B	.	.	.	.	1.37	.	*	F	1.10	2.10
Arg	722	.	.	B	.	.	.	.	1.91	.	*	F	1.10	4.38

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Ser	723	.	.	.	.	.	.	C	1.06	*	*	F	1.30	2.17
His	724	.	.	.	.	.	T	C	1.91	*	*	F	1.05	0.93
Pro	725	.	.	.	.	.	T	C	1.87	.	*	F	1.33	0.82
Gly	726	.	.	.	.	T	T	.	1.87	*	*	F	1.21	0.99
Val	727	.	.	B	.	.	T	.	1.41	*	*	F	1.84	1.21
Gln	728	.	.	B	.	.	.	.	1.71	.	*	F	1.77	0.77
Asn	729	.	.	B	.	T	T	.	1.50	*	.	F	2.80	1.26
Asp	730	.	.	.	.	T	T	.	0.90	*	.	F	1.92	2.66
Gly	731	.	.	.	.	T	T	.	0.66	.	.	F	1.64	1.27
Asn	732	.	.	B	.	.	T	.	0.70	.	*	F	0.81	0.80
Tyr	733	.	A	B	.	.	.	.	0.74	.	.	.	-0.32	0.39
Leu	734	.	A	B	.	.	.	.	0.43	*	.	.	-0.60	0.79
Ala	735	.	A	B	.	.	.	.	-0.16	*	.	.	-0.60	0.71
Leu	736	.	A	B	.	.	.	.	0.19	.	.	.	-0.40	0.46
Lys	737	.	A	B	.	.	.	.	-0.16	.	.	F	0.85	0.93
Thr	738	.	.	B	.	.	T	.	0.09	.	.	F	1.45	0.91
Ala	739	A	.	.	.	.	T	.	0.66	.	.	F	2.10	1.91
Asp	740	.	.	B	.	.	T	.	0.43	.	.	F	2.00	1.50
Gly	741	.	.	B	.	.	T	.	0.43	.	*	F	1.05	0.86
Gln	742	.	.	B	.	.	.	.	0.39	.	*	F	0.35	0.70
Tyr	743	.	.	B	.	.	.	.	0.36	.	*	.	0.30	0.67

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	744	.	.	B	.	.	.	.	0.94	.	*	.	-0.20	0.67
Leu	745	.	.	B	.	.	.	.	0.13	.	*	.	-0.40	0.63
Asn	746	.	.	B	.	.	T	.	-0.11	.	*	F	-0.05	0.33
Gly	747	.	.	.	.	T	T	.	-1.00	.	*	F	0.35	0.40
Asn	748	.	.	.	.	.	T	C	-1.06	.	*	.	0.00	0.34
Leu	749	.	.	.	.	.	T	C	-0.83	.	*	.	0.00	0.29
Ala	750	A	A	B	.	.	.	.	-0.91	.	*	.	-0.60	0.29
Ile	751	.	A	B	.	.	.	.	-0.91	*	*	.	-0.60	0.13
Ser	752	.	A	B	.	.	.	.	-0.57	*	.	.	-0.60	0.27
Ala	753	A	A	.	.	.	.	.	-0.57	*	*	.	-0.30	0.46
Ile	754	A	A	.	.	.	.	.	-0.64	*	.	.	0.45	1.09
Glu	755	A	A	.	.	.	.	.	-0.87	*	.	F	0.45	0.57
Gln	756	A	.	.	B	.	.	.	-0.83	.	*	F	0.45	0.47
Asp	757	A	.	.	B	.	.	.	-0.49	.	*	F	-0.15	0.49
Ile	758	A	.	.	B	.	.	.	-0.24	.	*	.	0.60	0.57
Leu	759	A	.	.	B	.	.	.	0.33	.	*	.	0.30	0.33
Val	760	A	.	.	B	.	.	.	-0.56	.	*	.	0.30	0.28
Lys	761	A	.	.	B	.	.	.	-1.37	.	*	F	-0.45	0.28
Gly	762	.	.	B	B	.	.	.	-1.32	.	*	F	-0.45	0.28
Thr	763	.	.	B	B	.	.	.	-0.68	.	*	F	0.45	0.76
Ile	764	.	.	B	B	.	.	.	-0.17	.	.	F	-0.15	0.59
Leu	765	.	.	B	B	.	.	.	0.34	.	*	.	-0.60	0.80

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Lys	766	.	.	B	B	.	.	.	0.00	.	*	F	-0.45	0.55
Tyr	767	.	.	B	.	.	T	.	-0.54	*	*	F	0.40	1.05
Ser	768	.	.	.	.	.	T	C	-0.82	*	*	F	0.45	0.89
Gly	769	.	.	.	.	.	T	C	-0.24	*	.	F	0.45	0.45
Ser	770	.	.	.	.	.	T	C	-0.24	.	*	F	0.15	0.42
Ile	771	.	A	B	.	.	.	.	-0.29	*	*	.	-0.60	0.26
Ala	772	.	A	B	.	.	.	.	0.07	*	.	.	-0.30	0.45
Thr	773	.	A	B	.	.	.	.	-0.44	*	*	.	0.30	0.66
Leu	774	.	A	B	.	.	.	.	-0.10	*	.	.	-0.30	0.77
Glu	775	A	A	.	.	.	.	.	-0.10	*		.	0.45	1.32
Arg	776	.	A	B	.	.	.	.	0.09	.	.	F	0.60	1.23
Leu	777	.	A	.	.	T	.	.	0.79	.	.	F	1.00	1.29
Gln	778	.	A	.	.	T	.	.	0.89	.	.	F	1.30	1.46
Ser	779	.	A	.	.	T	.	.	0.89	.	.	F	1.00	1.15
Phe	780	.	.	B	.	.	.	.	0.68	*	.	F	0.41	1.15
Arg	781	.	.	.	.	.	.	C	0.57	.	*	F	0.82	1.03
Pro	782	.	.	.	.	.	.	C	1.17	*	.	F	1.63	1.33
Leu	783	.	.	.	.	.	T	C	0.36	*	.	F	2.04	2.37
Pro	784	.	.	.	.	.	T	C	0.34	*	*	F	2.10	1.00
Glu	785	.	.	.	.	.	T	C	0.19	*	*	F	1.29	0.93
Pro	786	.	.	B	.	.	T	.	0.08	*	*	F	0.88	0.84
Leu	787	.	.	B	B	.	.	.	-0.52	.	*	F	0.27	0.94

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Thr	788	.	.	B	B	.	.	.	-0.52	.	*	.	-0.09	0.45
Val	789	.	.	B	B	.	.	.	-0.62	.	.	.	-0.60	0.24
Gln	790	.	.	B	B	.	.	.	-1.48	.	.	.	-0.60	0.42
Leu	791	.	.	B	B	.	.	.	-1.48	.	.	.	-0.60	0.21
Leu	792	.	.	B	B	.	.	.	-1.01	.	*	.	-0.60	0.45
Thr	793	.	.	B	B	.	.	.	-0.70	.	*	.	-0.60	0.26
Val	794	.	.	B	.	.	T	.	-0.70	*	.	F	0.25	0.54
Pro	795	.	.	B	.	.	T	.	-1.40	*	.	F	0.25	0.48
Gly	796	.	.	B	.	.	T	.	-0.80	*	.	F	-0.05	0.29
Glu	797	.	.	B	.	.	T	.	-0.20	.	*	F	0.25	0.60
Val	798	.	.	B	.	.	.	.	0.16	.	*	F	0.05	0.60
Phe	799	.	.	B	.	.	.	.	0.16	.	*	F	1.00	1.22
Pro	800	.	.	B	.	.	T	.	0.41	*	*	F	1.25	0.52
Pro	801	.	.	.	.	T	T	.	0.51	*	*	F	2.00	1.41
Lys	802	.	.	.	.	T	T	.	0.20	*	*	F	1.60	2.55
Val	803	.	.	B	.	.	T	.	0.36	.	*	F	2.00	2.38
Lys	804	.	.	B	B	.	.	.	0.36	.	*	F	0.80	1.33
Tyr	805	.	.	B	B	.	.	.	-0.29	.	*	.	0.00	0.58
Thr	806	.	.	B	B	.	.	.	-0.29	.	*	.	-0.20	0.58
Phe	807	.	.	B	B	.	.	.	-0.33	.	*	.	-0.40	0.45
Phe	808	.	.	B	B	.	.	.	0.52	*	*	.	-0.60	0.46
Val	809	.	.	B	.	.	T	.	-0.38	*	*	.	-0.20	0.53

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Pro	810	.	.	B	.	.	T	.	-0.13	.	*	F	-0.05	0.45
Asn	811	.	.	.	.	T	T	.	-0.52	.	*	F	1.25	0.88
Asp	812	.	.	.	.	T	T	.	-0.12	.	*	F	1.40	1.02
Val	813	A	.	.	.	.	.	.	-0.02	*	*	F	0.65	0.89
Asp	814	A	.	.	.	.	.	.	0.83	*	*	.	0.50	0.54
Phe	815	A	.	.	.	.	.	.	0.74	.	*	.	0.80	0.57
Ser	816	A	.	.	.	.	.	.	0.44	.	*	.	0.65	1.02
Met	817	A	.	.	.	.	.	.	0.49	.	*	.	1.40	0.82
Gln	818	A	.	.	.	.	T	.	1.34	.	*	F	2.20	1.89
Ser	819	.	.	.	.	.	T	C	1.46	.	*	F	3.00	2.44
Ser	820	.	.	.	.	.	T	C	1.57	.	*	F	2.70	4.84
Lys	821	A	.	.	.	.	T	.	1.56	.	*	F	2.20	2.82
Glu	822	A	.	.	.	.	.	.	1.84	.	*	F	1.70	3.04
Arg	823	A	.	.	B	.	.	.	1.84	*	*	F	1.20	3.27
Ala	824	A	.	.	B	.	.	.	1.26	*	*	F	0.90	2.63
Thr	825	.	.	B	B	.	.	.	0.67	*	*	F	0.60	1.06
Thr	826	.	.	B	B	.	.	.	0.62	*	*	F	-0.15	0.38
Asn	827	.	.	B	B	.	.	.	0.41	*	*	.	-0.60	0.65
Ile	828	.	.	B	B	.	.	.	-0.51	*	*	.	-0.60	0.70
Ile	829	.	.	B	B	.	.	.	-0.73	*	.	.	-0.60	0.40
Gln	830	.	A	B	.	.	.	.	-0.46	*	.	.	-0.60	0.21
Pro	831	.	A	B	.	.	.	.	-0.73	*	.	.	-0.60	0.40

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Leu	832	.	A	B	.	.	.	.	-0.73	*	*	.	-0.60	0.57
Leu	833	.	A	B	.	.	.	.	-0.13	.	.	.	-0.60	0.57
His	834	.	A	B	.	.	.	.	-0.10	.	*	.	-0.60	0.39
Ala	835	.	A	B	B	.	.	.	-0.91	.	*	.	-0.60	0.35
Gln	836	.	A	B	B	.	.	.	-1.04	.	.	.	-0.60	0.35
Trp	837	.	A	B	B	.	.	.	-0.23	.	.	.	-0.60	0.26
Val	838	.	A	B	B	.	.	.	0.29	.	*	.	-0.60	0.42
Leu	839	.	.	B	.	.	T	.	0.02	*	.	.	-0.20	0.26
Gly	840	.	.	.	.	T	T	.	0.61	*	.	.	0.45	0.33
Asp	841	.	.	.	.	T	T	.	-0.06	.	.	F	1.15	0.76
Trp	842	.	.	.	.	T	T	.	-0.07	.	.	F	2.00	0.50
Ser	843	.	.	.	.	.	T	C	0.49	*	.	F	2.05	0.67
Glu	844	.	.	.	.	T	T	.	0.99	.	.	F	2.50	0.54
Cys	845	.	.	.	.	T	T	.	0.67	.	.	F	1.65	0.74
Ser	846	.	.	.	.	T	T	.	0.32	.	.	F	2.00	0.30
Ser	847	.	.	.	.	T	.	.	0.02	.	.	F	1.55	0.17
Thr	848	.	.	.	.	T	.	.	-0.02	.	.	F	0.70	0.32
Cys	849	.	.	.	.	T	.	.	-0.31	.	.	F	0.45	0.24
Gly	850	.	.	.	.	T	T	.	0.36	*	.	.	0.20	0.18
Ala	851	.	.	.	.	T	T	.	0.77	.	.	.	0.20	0.22
Gly	852	.	.	.	.	T	T	.	1.18	.	.	.	0.50	0.81
Trp	853	.	.	.	.	T	T	.	1.18	*	.	.	1.25	1.60

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Gln	854	.	.	B	B	.	.	.	0.99	*	.	F	0.60	2.29
Arg	855	.	.	B	B	.	.	.	1.33	*	.	F	0.60	1.72
Arg	856	.	.	B	B	.	.	.	1.26	.	*	F	0.90	2.83
Thr	857	.	.	B	B	.	.	.	1.71	.	.	F	1.05	0.87
Val	858	.	.	B	B	.	.	.	2.00	.	.	.	1.20	0.87
Glu	859	.	.	B	B	.	.	.	1.79	.	.	.	1.50	0.75
Cys	860	.	.	.	.	T	.	.	1.38	.	*	.	2.40	0.80
Arg	861	.	.	.	.	T	.	.	0.92	.	.	F	3.00	1.44
Asp	862	.	.	.	.	.	T	C	1.23	.	*	F	2.55	0.82
Pro	863	.	.	.	.	T	T	.	1.50	.	*	F	2.60	2.66
Ser	864	.	.	.	.	T	T	.	1.20	.	*	F	2.30	1.37
Gly	865	.	.	.	.	T	T	.	1.28	.	.	F	1.70	1.10
Gln	866	A	.	.	.	.	.	.	0.86	.	*	F	0.05	0.72
Ala	867	.	.	B	.	.	.	.	0.19	.	*	F	0.05	0.78
Ser	868	.	.	B	.	.	.	.	0.40	.	*	.	-0.10	0.42
Ala	869	A	.	.	.	.	.	.	0.74	.	*	.	-0.10	0.39
Thr	870	A	.	.	.	.	T	.	0.50	*	.	.	0.70	0.77
Cys	871	A	.	.	.	.	T	.	-0.31	*	.	.	0.70	0.58
Asn	872	A	.	.	.	.	T	.	0.32	*	.	.	0.10	0.48
Lys	873	A	.	.	.	.	T	.	0.41	.	.	F	0.85	0.66
Ala	874	A	.	.	.	.	.	.	1.00	*	.	F	0.80	1.90
Leu	875	A	.	.	.	.	.	.	1.31	*	.	F	1.10	2.05

SUBSTITUTE SHEET (RULE 26)

Res	Pos.	Garni.. Alpha	Chou-... Alpha	Garni.. Beta	Chou-... Beta	Garni.. Turn	Chou-... Turn	Garni.. Coil	Kyte-... Hydro...	Eisen... Alpha	Eisen... Beta	Karpl... Flexi...	James... Antig...	Emini Surfa...
Lys	876	A	.	.	.	.	T	.	1.39	.	.	F	1.30	1.71
Pro	877	A	.	.	.	.	T	.	1.43	.	.	F	1.30	1.71
Glu	878	A	.	.	.	.	T	.	1.18	.	.	F	1.30	4.14
Asp	879	A	.	.	.	.	T	.	1.10	.	.	F	1.30	3.20
Ala	880	A	.	.	.	.	.	.	1.91	.	.	F	1.10	1.11
Lys	881	A	.	.	.	.	T	.	1.57	.	.	F	1.30	1.11
Pro	882	A	.	.	.	.	T	.	1.78	*	.	F	1.15	0.89
Cys	883	A	.	.	.	.	T	.	0.97	*	.	F	1.30	1.53
Glu	884	A	.	.	.	.	T	.	0.30	.	.	F	1.15	0.63
Ser	885	A	A	.	.	.	.	.	0.68	*	.	F	-0.15	0.22
Gln	886	.	A	B	.	.	.	.	-0.18	*	.	F	-0.15	0.63
Leu	887	.	A	B	.	.	.	.	-0.36	.	.	.	-0.30	0.30
Cys	888	.	A	B	.	.	.	.	-0.08	.	.	.	-0.60	0.29
Pro	889	.	A	B	.	.	.	.	-0.47	.	.	.	-0.60	0.21
Leu	890	.	.	B	.	.	.	.	-0.56	.	.	.	-0.40	0.33

Detailed Description

By screening cDNA libraries with cDNA encoding the anti-angiogenic domain of TSP-1, the present inventors have identified two novel proteins, METH1 and METH2 (also called VEGA-1 and VEGA-2, respectively, for vascular endothelial growth antagonist) which contain the anti-angiogenic domain of TSP-1, a metalloproteinase domain, and a disintegrin-like domain. The present inventors have demonstrated that both METH1 and METH2 have anti-angiogenic activity.

Thus, the present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding a METH1 polypeptide having the amino acid sequence shown in SEQ ID NO:2, which was determined by sequencing a cloned cDNA. The METH1 protein of the present invention shares sequence homology with thrombospondin-1 and pNPI. The nucleotide sequence shown in SEQ ID NO:1 was obtained by sequencing a cDNA clone, which was deposited on January 15, 1998 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, and given accession number 209581. The cDNA clone contained in ATCC Deposit No. 209581 contains a METH1 sequence, encoding amino acids 1 to 950 of SEQ ID NO:2.

The present invention also provides isolated nucleic acid molecules comprising a polynucleotide encoding a METH2 polypeptide having the amino acid sequence shown in SEQ ID NO:4, which was partially determined by sequencing a cloned cDNA. The METH2 protein of the present invention shares sequence homology with thrombospondin-1 and pNPI. The nucleotide sequence shown in SEQ ID NO:3 was partially obtained by sequencing a cDNA clone, which was deposited on January 15, 1998 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, and given accession number 209582. The cDNA clone contained in ATCC Deposit No. 209582 contains a partial METH2 sequence, encoding amino acids 112-890 of SEQ ID NO:4.

Nucleic Acid Molecules

Some of the nucleotide sequences determined by sequencing a DNA molecule herein were determined using an automated DNA sequencer (such as the Model 373 from Applied Biosystems, Inc.), and all amino acid sequences of polypeptides encoded by DNA molecules determined herein were predicted by translation of a DNA sequence determined as above. Therefore, as is known in the art for any DNA sequence determined by this automated approach, any nucleotide sequence determined herein may contain some errors. Nucleotide sequences determined by automation are typically at least about 90% identical, more typically at least about 95% to at least about 99.9% identical to the actual nucleotide sequence of the sequenced DNA molecule. The actual sequence can be more precisely determined by other approaches including manual DNA sequencing methods well known in the art. As is also known in the art, a single insertion or deletion in a determined nucleotide sequence compared to the actual sequence will cause a frame shift in translation of the nucleotide sequence such that the predicted amino acid sequence encoded by a determined nucleotide sequence will be completely different from the amino acid sequence actually encoded by the sequenced DNA molecule, beginning at the point of such an insertion or deletion.

Using the information provided herein, such as the nucleotide sequence in SEQ ID NO: 1 or SEQ ID NO:3, a nucleic acid molecule of the present invention encoding a METH1 or METH2 polypeptide may be obtained using standard cloning and screening procedures, such as those for cloning cDNAs using mRNA as starting material. Illustrative of the invention, the nucleic acid molecule described in SEQ ID NO:1 was discovered in a cDNA library derived from human heart and the nucleic acid molecule described in SEQ ID NO:3 was discovered in a cDNA library derived from human lung. The determined nucleotide sequence of the METH1 cDNA of SEQ ID NO:1 contains an open reading frame encoding

a protein of about 950 amino acid residues, including a predicted leader sequence of about 28 amino acid residues. The present inventors have determined that the nucleotide sequence of the METH2 cDNA of SEQ ID NO:3 contains an open reading frame encoding a protein of about 890 amino acid residues, including a predicted leader sequence of about 23 amino acid residues.

The present invention also provides the mature form(s) of the METH1 and METH2 proteins of the present invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species on the protein. Further, it has long been known that the cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide. Therefore, the present invention provides a nucleotide sequence encoding the mature METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in the host identified as ATCC Deposit No. 209581 and as shown in SEQ ID NO:2. The present invention also provides a nucleotide sequence encoding the mature METH2 polypeptide having the amino acid sequence as shown in SEQ ID NO:4. By the mature METH1 protein having the amino acid sequence encoded by the cDNA clone contained in the host identified as ATCC Deposit No. 209581 is meant the mature form(s) of the METH1 protein produced by expression in a mammalian cell (e.g., COS cells, as described below) of the complete open reading frame encoded by the human DNA sequence of the clone contained in the vector in the deposited host. As indicated below, the mature METH1 having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581 may or may not differ from the predicted "mature" METH1 protein shown in SEQ ID NO:2 (amino acids from about 29 to about 950) depending on the accuracy of

the predicted cleavage site based on computer analysis; and the mature METH2 may or may not differ from the predicted "mature" METH2 protein shown in SEQ ID NO: 4 (amino acids from about 24 to about 890) depending on the accuracy of the predicted cleavage site based on computer analysis.

Methods for predicting whether a protein has a secretory leader as well as the cleavage point for that leader sequence are available. For instance, the methods of McGeoch (*Virus Res.* 3:271-286 (1985)) and von Heinje (*Nucleic Acids Res.* 14:4683-4690 (1986)) can be used. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. von Heinje, *supra*. However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the predicted amino acid sequence of the complete METH1 and METH2 polypeptides of the present invention were analyzed by a computer program ("PSORT") (K. Nakai and M. Kanehisa, *Genomics* 14:897-911 (1992)), which is an expert system for predicting the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis by the PSORT program predicted the cleavage site between amino acids 28 and 29 in SEQ ID NO:2 and amino acids 23 and 24 in SEQ ID NO:4. Thereafter, the complete amino acid sequences were further analyzed by visual inspection, applying a simple form of the (-1,-3) rule of von Heinje. von Heinje, *supra*. Thus, the leader sequence for the METH1 protein is predicted to consist of amino acid residues from about 1 to about 28 in SEQ ID NO:2, while the mature METH1 protein is predicted to consist of residues from about 29 to about 950; and the leader sequence for the METH2 protein is predicted to consist of amino acid residues from about 1 to about 23 in SEQ ID NO:4, while the mature METH2 protein is predicted to consist of residues from about 24 to about 890. An alternative predicted mature METH1 protein consists of residues 30 to 950 in SEQ ID NO:2.

As one of ordinary skill would appreciate, due to the possibilities of sequencing errors, as well as the variability of cleavage sites for leaders in different known proteins, the predicted METH1 polypeptide encoded by the deposited cDNA comprises about 950 amino acids, but may be anywhere in the range of 910-990 amino acids; and the predicted leader sequence of this protein is about 28 amino acids, but may be anywhere in the range of about 18 to about 38 amino acids. Also, the predicted METH2 polypeptide comprises about 890 amino acids, but may be anywhere in the range of 850 to about 930 amino acids; and the predicted leader sequence of this protein is about 23 amino acids, but may be anywhere in the range of about 13 to about 33 amino acids.

As indicated, nucleic acid molecules of the present invention may be in the form of RNA, such as mRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced synthetically. The DNA may be double-stranded or single-stranded. Single-stranded DNA or RNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand.

By "isolated" nucleic acid molecule(s) is intended a nucleic acid molecule, DNA or RNA, which has been removed from its native environment. For example, recombinant DNA molecules contained in a vector are considered isolated for the purposes of the present invention. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the DNA molecules of the present invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically.

Isolated nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) shown in SEQ ID NO:1; DNA molecules comprising the coding sequence for the mature METH1 protein; and DNA molecules which comprise a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode

the METH1 protein. Also included are DNA molecules comprising an open reading frame (ORF) shown in SEQ ID NO:3; DNA molecules comprising the coding sequence for the mature METH2 protein; and DNA molecules which comprise a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode the METH2 protein. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.

In another aspect, the invention provides isolated nucleic acid molecules encoding the METH1 or METH2 polypeptides having an amino acid sequence as encoded by the cDNA clones contained in the plasmids deposited as ATCC Deposit No. 209581 on January 15, 1998 or ATCC Deposit No. 209582 on January 15, 1998, respectively. In a further embodiment, nucleic acid molecules are provided encoding the mature METH1 or METH2 polypeptide or the full-length METH1 or METH2 polypeptide lacking the N-terminal methionine. The invention also provides an isolated nucleic acid molecule having the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:3 or the nucleotide sequence of the METH1 or METH2 cDNA contained in the above-described deposited clones, or a nucleic acid molecule having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful as probes for gene mapping, by *in situ* hybridization with chromosomes, and for detecting expression of the METH1 or METH2 gene in human tissue, for instance, by Northern blot analysis.

The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated nucleic acid molecule having the nucleotide sequence of the deposited cDNA or the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:3 is intended fragments at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700,

750, 800, 850, 900, 950, 1000, 1050, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, or 3000 nt in length are also useful according to the present invention as are fragments corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or as shown in SEQ ID NO:1 or SEQ ID NO:3. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of the deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:1 or SEQ ID NO:3.

Preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding epitope-bearing portions of the METH1 or METH2 protein. Methods for determining epitope-bearing portions of the METH1 and METH2 proteins are described in detail below.

Other preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding: the metalloprotease domain of METH1, amino acids 235 to 459 in SEQ ID NO:2; the disintegrin domain of METH1, amino acids 460 to 544 in SEQ ID NO:2; the first TSP-like domain of METH1, amino acids 545 to 598 in SEQ ID NO:2; the second TSP-like domain of METH1, amino acids 841 to 894 in SEQ ID NO:2; the third TSP-like domain of METH1, amino acids 895 to 934 in SEQ ID NO:2; amino acids 536 to 613 in SEQ ID NO:2; amino acids 549 to 563 in SEQ ID NO:2; the metalloprotease domain of METH2, amino acids 214 to 439 in SEQ ID NO:4; the disintegrin domain of METH2, amino acids 440 to 529 in SEQ ID NO:4; the first TSP-like domain of METH2, amino acids 530 to 583 in SEQ ID NO:4; the second TSP-like domain of METH2, amino acids 837 to 890 in SEQ ID NO:4; amino acids 280 to 606 in SEQ ID NO:4; and amino acids 529 to 548 in SEQ ID NO:4.

In addition, the present inventors have identified the following cDNA clones related to portions of the sequence shown in SEQ ID NO:1: HOUCQ17RA (SEQ ID NO:14), HPLBM11R (SEQ ID NO:15), HGBI07R (SEQ ID NO:16), HNTMA49R (SEQ ID NO:17), HNALE27R (SEQ ID NO:18), and HIBDB45R (SEQ ID NO:19).

The following public ESTs, which relate to portions of SEQ ID NO:1, have also been identified: D67076 (SEQ ID NO:20), AB001735 (SEQ ID NO:21), X14787 (SEQ ID NO:22), U64857 (SEQ ID NO:23), X04665 (SEQ ID NO:24), M64866 (SEQ ID NO:25), L07803 (SEQ ID NO:26), U08006 (SEQ ID NO:27), M16974 (SEQ ID NO:28), L13855 (SEQ ID NO:29), AL021529 (SEQ ID NO:30), D86074 (SEQ ID NO:31), L05390 (SEQ ID NO:32), Z69361 (SEQ ID NO:33), X99599 (SEQ ID NO:34), AF018073 (SEQ ID NO:35), L23760 (SEQ ID NO:36), Z46970 (SEQ ID NO:37), AC004449 (SEQ ID NO:38), Z69589 (SEQ ID NO:39), Z22279 (SEQ ID NO:40), and X17524 (SEQ ID NO:41).

The present inventors have also identified the following cDNA clones related to portions of SEQ ID NO:3: HCE4D69FP02 (SEQ ID NO:42), HIBDB45F (SEQ ID NO:43), HKIXH64R (SEQ ID NO:44), HIBDB45R (SEQ ID NO:19), HCE3Z95R (SEQ ID NO:45), HTLEQ90R (SEQ ID NO:46), HMWEF45R (SEQ ID NO:47), HTOFC34RA (SEQ ID NO:48), HHFDI20R (SEQ ID NO:49), HMSHY47R (SEQ ID NO:50), HCESF90R (SEQ ID NO:51), HMCAO46R (SEQ ID NO:52), HTTAQ67R (SEQ ID NO:53), HFKCF19F (SEQ ID NO:54), HMCAS31R (SEQ ID NO:55), HMWGP26R (SEQ ID NO:56), HLHTP36R (SEQ ID NO:57), HE8AN11R (SEQ ID NO:58), HEONN73R (SEQ ID NO:59), HBNBG53R (SEQ ID NO:60), and HMSCH94R (SEQ ID NO:61).

The following public ESTs, which relate to portions of the sequence shown in SEQ ID NO:3, have also been identified: D67076 (SEQ ID NO:20), AB001735 (SEQ ID NO:21), AB005287 (SEQ ID NO:62), X87619 (SEQ ID NO:63), X14787 (SEQ ID NO:22), X04665 (SEQ ID NO:24), M87276 (SEQ ID NO:64), M62458 (SEQ ID NO:65), AB002364 (SEQ ID NO:66), AB005297 (SEQ ID NO:67), X69161 (SEQ ID NO:68), X16619 (SEQ ID NO:69), I36448 (SEQ ID NO:70), L12260 (SEQ ID NO:71), I36352 (SEQ ID NO:72), X15898 (SEQ ID NO:73), I07789 (SEQ ID NO:74), I08144 (SEQ ID NO:75) U31814 (SEQ ID NO:76), and AF001444 (SEQ ID NO:77).

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of METH1 or METH2 coding sequence, but do not comprise all or a portion of any METH1 or METH2 intron. In another embodiment, the nucleic acid comprising METH1 or METH2 coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the METH1 or METH2 gene in the genome).

In another aspect, the invention provides an isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent hybridization conditions to a portion of the polynucleotide in a nucleic acid molecule of the invention described above, for instance, the cDNA clones contained in ATCC Deposit No. 209581 or ATCC Deposit No. 209582. By "stringent hybridization conditions" is intended overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (750 mM NaCl, 75mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

By a polynucleotide which hybridizes to a "portion" of a polynucleotide is intended a polynucleotide (either DNA or RNA) hybridizing to at least about 15 nucleotides (nt), and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably about 30, 40, 50, 60 or 70 nt of the reference polynucleotide. These are useful as diagnostic probes and primers as discussed above and in more detail below.

By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., the deposited cDNAs or the nucleotide sequence as shown in SEQ ID NO:1 or SEQ ID NO:3). Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3′ terminal poly(A) tract of the METH1 or METH2 cDNA shown in SEQ ID NO:1 and SEQ ID NO:3,

respectively) or to a complementary stretch of T (or U) resides, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

Also contemplated are nucleic acid molecules that hybridize to the METH1 or METH2 polynucleotides at moderately high stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, moderately high stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The METH1 or METH2 polynucleotide can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, METH1 or METH2 polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the METH1 or METH2 polynucleotides can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. METH1 or METH2 polynucleotides may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

"SEQ ID NO:1" refers to a METH1 polynucleotide sequence while "SEQ ID NO:2" refers to a METH1 polypeptide sequence. "SEQ ID NO:3" refers to a METH2 polynucleotide sequence while "SEQ ID NO:4" refers to a METH2 polypeptide sequence.

As indicated, nucleic acid molecules of the present invention which encode a METH1 or METH2 polypeptide may include, but are not limited to, those encoding the amino acid sequence of the mature polypeptide, by itself; the coding sequence for the mature polypeptide and additional sequences, such as those encoding the leader or secretory sequence, such as a pre-, or pro- or prepro-protein sequence; the coding sequence of the mature polypeptide, with or without the aforementioned additional coding sequences, together with additional, non-coding sequences, including for example, but not limited to introns and non-coding 5′ and 3′ sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals, for example - ribosome binding and stability of mRNA;

an additional coding sequence which codes for additional amino acids, such as those which provide additional functionalities. Thus, the sequence encoding the polypeptide may be fused to a marker sequence, such as a sequence encoding a peptide which facilitates purification of the fused polypeptide. In certain preferred embodiments of this aspect of the invention, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (Qiagen, Inc.), among others, many of which are commercially available. As described in Gentz *et al., Proc. Natl. Acad. Sci. USA 86*:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. The "HA" tag is another peptide useful for purification which corresponds to an epitope derived from the influenza hemagglutinin protein, which has been described by Wilson *et al., Cell 37*:767-778 (1984). As discussed below, other such fusion proteins include the METH1 or METH2 fused to Fc at the N- or C-terminus.

The present invention further relates to variants of the nucleic acid molecules of the present invention, which encode portions, analogs or derivatives of the METH1 or METH2 protein. Variants may occur naturally, such as a natural allelic variant. By an "allelic variant" is intended one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. Lewin, B., ed., *Genes II*, John Wiley & Sons, New York (1985). Non-naturally occurring variants may be produced using art-known mutagenesis techniques.

Such variants include those produced by nucleotide substitutions, deletions or additions, which may involve one or more nucleotides. The variants may be altered in coding regions, non-coding regions, or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the METH1 or METH2 protein or portions thereof. Also especially preferred in this regard are conservative substitutions.

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 95%

identical, and more preferably at least 96%, 97%, 98% or 99% identical to: a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:2; a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:2, but lacking the N-terminal methionine; a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 29 to about 950 in SEQ ID NO:2; a nucleotide sequence encoding the polypeptide having the amino acid sequence at position from about 30 to about 950 in SEQ ID NO:2; a nucleotide sequence encoding the polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581; a nucleotide sequence encoding the mature METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581; a nucleotide sequence encoding amino acids 235 to 459 in SEQ ID NO:2 (the metalloprotease domain of METH1); a nucleotide sequence encoding amino acids 460 to 544 in SEQ ID NO:2 (the disintegrin domain of METH1); a nucleotide sequence encoding amino acids 545 to 598 in SEQ ID NO:2 (the first TSP-like domain of METH1); a nucleotide sequence encoding amino acids 841 to 894 in SEQ ID NO:2 (the second TSP-like domain of METH1); a nucleotide sequence encoding amino acids 895 to 934 in SEQ ID NO:2 (the third TSP-like domain of METH1); a nucleotide sequence encoding amino acids 536 to 613 in SEQ ID NO:2; a nucleotide sequence encoding amino acids 549 to 563 in SEQ ID NO:2; a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:4; a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:4, but lacking the N-terminal methionine; a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 24 to about 890 in SEQ ID NO:4; a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 112 to about 890 in SEQ ID NO:4; a nucleotide sequence encoding the polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582; a nucleotide sequence encoding the mature METH2 polypeptide having the amino

acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582; a nucleotide sequence encoding amino acids 214 to 439 in SEQ ID NO:4 (the metalloprotease domain of METH2); a nucleotide sequence encoding amino acids 440 to 529 in SEQ ID NO:4 (the disintegrin domain of METH2); a nucleotide sequence encoding amino acids 530 to 583 in SEQ ID NO:4 (the first TSP-like domain of METH2); a nucleotide sequence encoding amino acids 837 to 890 in SEQ ID NO:4 (the second TSP-like domain of METH2); a nucleotide sequence encoding amino acids 280 to 606 in SEQ ID NO:4; a nucleotide sequence encoding amino acids 529 to 548 in SEQ ID NO:4; or a nucleotide sequence complementary to any of the above nucleotide sequences .

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a METH1 or METH2 polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the METH1 or METH2 polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mutations of the reference sequence may occur at the 5′ or 3′ terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular nucleic acid molecule is at least 95%, 96%, 97%, 98% or 99% identical to, for instance, the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:3 or to the nucleotide sequence of the deposited cDNA clones can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis

Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics 2*: 482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag *et al.*, *Comp. Appl. Biosci. 6*:237-245 (1990). In a sequence alignment, the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is

matched/aligned is determined by the results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and, therefore, the FASTDB alignment does not show a match/alignment of the first 10 bases at the 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence), so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal, so that there are no bases on the 5' or 3' ends of the subject sequence which are not matched/aligned with the query. In this case, the percent identity calculated by FASTDB is not manually corrected. One again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The present application is directed to nucleic acid molecules at least 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3 or to the nucleic acid sequence of the deposited cDNAs, irrespective of whether they encode a polypeptide having METH1 or METH2 activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having METH1 or METH2 activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a

hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having METH1 or METH2 activity include, *inter alia,* (1) isolating the METH1 or METH2 gene or allelic variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the METH1 or METH2 gene, as described in Verma *et al., Human Chromosomes: A Manual of Basic Techniques*, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting METH1 or METH2 mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3 or to a nucleic acid sequence of the deposited cDNAs which do, in fact, encode a polypeptide having METH1 or METH2 protein activity. By "a polypeptide having METH1 activity" is intended polypeptides exhibiting METH1 activity in a particular biological assay. For example, METH1 protein activity can be measured using the chorioallantoic membrane assay (Iruela-Arispe *et al., Thrombosis and Haemostasis 78(1)*:672-677 (1997)) or the cornea pocket assay (Tolsma *et al., J. Cell. Biol. 122*:497-511 (1993)), both described in Example 4, below. By "a polypeptide having METH2 activity" is intended polypeptides exhibiting METH2 activity in a particular biological assay. For example, METH2 protein activity can also be measured using the chorioallantoic membrane assay (Iruela-Arispe *et al., Thrombosis and Haemostasis 78(1)*:672-677 (1997)) or the cornea pocket assay (Tolsma *et al., J. Cell. Biol. 122*:497-511 (1993)), both described in Example 4, below.

Briefly, in the chorioallantoic assay, the potentially anti-angiogenic compound of interest is added to type I collagen pellets (Vitrogen), along with an angiogenic growth factor, such as bFGF. The samples are mixed and placed onto nylon meshes, and allowed to polymerize. After polymerization is complete, the meshes are placed onto the chorioallantoic membrane of 12 day old chick embryos and placed at 37°C for 24 hours. The embryos then injected with a fluorescent

agent, such as FITC-dextran, and the meshes are fixed and mounted for observation under a fluorescent microscope.

In the cornea pocket assay, hydron pellets containing the compound of interest and an angiogenic growth factor, such as bFGF, are implanted 1 to 2mm from the limbus of the cornea of rats or mice. Response is examined after a period of time, for example 5 days. The extent of angiogenesis is evaluated by measuring the capillaries migrating from the limb of the cornea.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 95%, 96%, 97%, 98%, or 99% identical to a nucleic acid sequence of the deposited cDNAs or a nucleic acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3 will encode a polypeptide "having METH1 or METH2 protein activity." In fact, since degenerate variants of these nucleotide sequences all encode the same polypeptide, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having METH1 or METH2 protein activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. *et al.*, "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science 247:*1306-1310 (1990), wherein the authors indicate that proteins are surprisingly tolerant of amino acid substitutions.

Vectors and Host Cells

The present invention also relates to vectors which include the isolated DNA molecules of the present invention, host cells which are genetically engineered with the recombinant vectors, and the production of METH1 or METH2 polypeptides or fragments thereof by recombinant techniques.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

The DNA insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac, trp* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase or neomycin resistance for eukaryotic cell culture and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from Qiagen; pBS vectors, Phagescript vectors, Bluescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

In addition to the use of expression vectors in the practice of the present invention, the present invention further includes novel expression vectors comprising operator and promoter elements operatively linked to nucleotide sequences encoding a protein of interest. One example of such a vector is pHE4-5 which is described in detail below.

As summarized in Figures 8 and 9, components of the pHE4-5 vector (SEQ ID NO:12) include: 1) a neomycinphosphotransferase gene as a selection marker, 2) an *E. coli* origin of replication, 3) a T5 phage promoter sequence, 4) two *lac* operator sequences, 5) a Shine-Delgarno sequence, 6) the lactose operon repressor gene (*lac*Iq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences were made synthetically. Synthetic production of nucleic acid sequences is well known in the art. CLONTECH 95/96 Catalog, pages 215-216, CLONTECH, 1020 East Meadow Circle, Palo Alto, CA 94303. A nucleotide sequence encoding METH1 (SEQ ID NO:2) or METH2 (SEQ ID NO:4), is operatively linked to the promoter and operator by inserting the nucleotide sequence between the NdeI and Asp718 sites of the pHE4-5 vector.

As noted above, the pHE4-5 vector contains a *lac*Iq gene. *Lac*Iq is an allele of the *lac*I gene which confers tight regulation of the *lac* operator. Amann, E. *et al.*, *Gene 69*:301-315 (1988); Stark, M., *Gene 51*:255-267 (1987). The *lac*Iq gene encodes a repressor protein which binds to *lac* operator sequences and blocks transcription of down-stream (*i.e.*, 3') sequences. However, the *lac*Iq gene

product dissociates from the *lac* operator in the presence of either lactose or certain lactose analogs, *e.g.*, isopropyl B-D-thiogalactopyranoside (IPTG). METH1 or METH2 thus is not produced in appreciable quantities in uninduced host cells containing the pHE4-5 vector. Induction of these host cells by the addition of an agent such as IPTG, however, results in the expression of the METH1 or METH2 coding sequence.

The promoter/operator sequences of the pHE4-5 vector (SEQ ID NO:13) comprise a T5 phage promoter and two *lac* operator sequences. One operator is located 5' to the transcriptional start site and the other is located 3' to the same site. These operators, when present in combination with the *lac*Iq gene product, confer tight repression of down-stream sequences in the absence of a *lac* operon inducer, *e.g.*, IPTG. Expression of operatively linked sequences located down-stream from the *lac* operators may be induced by the addition of a *lac* operon inducer, such as IPTG. Binding of a *lac* inducer to the *lac*Iq proteins results in their release from the *lac* operator sequences and the initiation of transcription of operatively linked sequences. *Lac* operon regulation of gene expression is reviewed in Devlin, T., TEXTBOOK OF BIOCHEMISTRY WITH CLINICAL CORRELATIONS, 4th Edition (1997), pages 802-807.

The pHE4 series of vectors contain all of the components of the pHE4-5 vector except for the METH1 or METH2 coding sequence. Features of the pHE4 vectors include optimized synthetic T5 phage promoter, *lac* operator, and Shine-Delgarno sequences. Further, these sequences are also optimally spaced so that expression of an inserted gene may be tightly regulated and high level of expression occurs upon induction.

Among known bacterial promoters suitable for use in the production of proteins of the present invention include the *E. coli lac*I and *lac*Z promoters, the T3 and T7 promoters, the *gpt* promoter, the lambda PR and PL promoters and the *trp* promoter. Suitable eukaryotic promoters include the CMV immediate early promoter, the HSV thymidine kinase promoter, the early and late SV40 promoters, the promoters of retroviral LTRs, such as those of the Rous Sarcoma

Virus (RSV), and metallothionein promoters, such as the mouse metallothionein-I promoter.

The pHE4-5 vector also contains a Shine-Delgarno sequence 5' to the AUG initiation codon. Shine-Delgarno sequences are short sequences generally located about 10 nucleotides up-stream (*i.e.*, 5') from the AUG initiation codon. These sequences essentially direct prokaryotic ribosomes to the AUG initiation codon.

Thus, the present invention is also directed to expression vector useful for the production of the proteins of the present invention. This aspect of the invention is exemplified by the pHE4-5 vector (SEQ ID NO:12).

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other methods. Such methods are described in many standard laboratory manuals, such as Davis *et al.*, *Basic Methods In Molecular Biology* (1986).

The polypeptide may be expressed in a modified form, such as a fusion protein, and may include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability and to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize proteins. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is

thoroughly advantageous for use in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified in the advantageous manner described. This is the case when the Fc portion proves to be a hindrance to use in therapy and diagnosis, for example when the fusion protein is to be used as an antigen for immunizations. In drug discovery, for example, human proteins, such as the hIL5-receptor, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett *et al.*, *J. Mol. Recognition 8*:52-58 (1995) and K. Johanson *et al.*, *J. of Biol. Chem. 270(16)*:9459-9471 (1995).

The METH1 or METH2 protein can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Polypeptides of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes.

METH1 and METH2 Polypeptides and Fragments

The invention further provides an isolated METH1 polypeptide having the amino acid sequence encoded by the deposited cDNA, or the amino acid sequence in SEQ ID NO:2, or a peptide or polypeptide comprising a portion of the above polypeptides. The invention also provides an isolated METH2 polypeptide having the amino acid sequence encoded by the deposited cDNA, or the amino acid sequence in SEQ ID NO:4, or a peptide or polypeptide comprising a portion of the above polypeptides.

METH1 or METH2 polypeptides can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The METH1 or METH2 polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in the METH1 or METH2 polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given METH1 or METH2 polypeptide. Also, a given METH1 or METH2 polypeptide may contain many types of modifications. METH1 or METH2 polypeptides may be branched , for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic METH1 or METH2 polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation,

demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter *et al.*, *Meth Enzymol 182*:626-646 (1990); Rattan *et al.*, *Ann NY Acad Sci 663*:48-62 (1992).)

It will be recognized in the art that some amino acid sequences of the METH1 and METH2 polypeptides can be varied without significant effect of the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the protein which determine activity.

The present inventors have shown that METH1 and METH2 inhibit angiogenesis *in vitro* and *in vivo*. METH1 and METH2 each contain a metalloprotease domain, a disintegrin domain, and TSP-like domains. The metalloprotease domain may be catalytically active. The disintegrin domain may play a role in inhibiting angiogenesis by interacting with integrins, since integrins are essential for the mediation of both proliferative and migratory signals. The present inventors have shown that peptides derived from the TSP-like domains of METH1 and METH2 inhibit angiogenesis *in vitro* and *in vivo*.

Thus, the invention further includes variations of the METH1 polypeptide which show substantial METH1 polypeptide activity or which include regions of METH1 protein such as the protein portions discussed below; and variations of the METH2 polypeptide which show substantial METH2 polypeptide activity or which include regions of METH2 protein such as the protein portions discussed below. Such mutants include deletions, insertions, inversions, repeats, and type

substitutions. As indicated above, guidance concerning which amino acid changes are likely to be phenotypically silent can be found in Bowie, J.U., *et al.*, "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science 247:*1306-1310 (1990).

Thus, the fragment, derivative or analog of the polypeptide of SEQ ID NO:2 or SEQ ID NO:4, or that encoded by the deposited cDNA, may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in proteins with reduced positive charge to improve the characteristics of the METH1 or METH2 proteins. The prevention of aggregation is highly desirable. Aggregation of proteins not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic. (Pinckard *et al.*, *Clin. Exp. Immunol. 2*:331-340 (1967); Robbins *et al., Diabetes 36*:838-845 (1987); Cleland *et al., Crit. Rev. Therapeutic Drug Carrier Systems 10*:307-377 (1993)).

As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 3).

TABLE 3. Conservative Amino Acid Substitutions.

Aromatic	Phenylalanine Tryptophan Tyrosine
Hydrophobic	Leucine Isoleucine Valine
Polar	Glutamine Asparagine
Basic	Arginine Lysine Histidine
Acidic	Aspartic Acid Glutamic Acid
Small	Alanine Serine Threonine Methionine Glycine

Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions for any given METH1 or METH2 polypeptide will not be more than 50, 40, 30, 20, 10, 5, or 3.

Amino acids in the METH1 and METH2 proteins of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science 244*:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as *in vitro* or *in vivo* inhibition of angiogenesis. Sites that are critical for inhibition of angiogenesis can also be determined by structural analysis such as crystallization, nuclear magnetic

resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol. 224*:899-904 (1992) and de Vos *et al.*, *Science 255*:306-312 (1992)).

The polypeptides of the present invention are preferably provided in an isolated form. By "isolated polypeptide" is intended a polypeptide removed from its native environment. Thus, a polypeptide produced and/or contained within a recombinant host cell is considered isolated for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host cell or from a native source. For example, a recombinantly produced version of the METH1 or METH2 polypeptide can be substantially purified by the one-step method described in Smith and Johnson, *Gene 67*:31-40 (1988).

The polypeptides of the present invention include the METH1 polypeptide encoded by the deposited cDNA including the leader; the mature METH1 polypeptide encoded by the deposited the cDNA minus the leader (i.e., the mature protein); a polypeptide comprising amino acids about 1 to about 950 in SEQ ID NO:2; a polypeptide comprising amino acids about 2 to about 950 in SEQ ID NO:2; a polypeptide comprising amino acids about 29 to about 950 in SEQ ID NO:2; a polypeptide comprising amino acids about 30 to about 950 in SEQ ID NO:2; a polypeptide comprising the metalloprotease domain of METH1, amino acids 235 to 459 in SEQ ID NO:2; a polypeptide comprising the disintegrin domain of METH1, amino acids 460 to 544 in SEQ ID NO:2; a polypeptide comprising the first TSP-like domain of METH1, amino acids 545 to 598 in SEQ ID NO:2; a polypeptide comprising the second TSP-like domain of METH1, amino acids 841 to 894 in SEQ ID NO:2; a polypeptide comprising the third TSP-like domain of METH1, amino acids 895 to 934 in SEQ ID NO:2; a polypeptide comprising amino acids 536 to 613 in SEQ ID NO:2; a polypeptide comprising amino acids 549 to 563 in SEQ ID NO:2; the METH2 polypeptide encoded by the deposited cDNA including the leader; the mature METH2 polypeptide encoded by the deposited the cDNA minus the leader (i.e., the mature protein); a polypeptide comprising amino acids about 1 to about 890 in SEQ ID NO:4; a

polypeptide comprising amino acids about 2 to about 890 in SEQ ID NO:4; a polypeptide comprising amino acids about 24 to about 890 in SEQ ID NO:4; a polypeptide comprising amino acids about 112 to about 890 in SEQ ID NO:4; a polypeptide comprising the metalloprotease domain of METH2, amino acids 214 to 439 in SEQ ID NO:4; a polypeptide comprising the disintegrin domain of METH2, amino acids 440 to 529 in SEQ ID NO:4; a polypeptide comprising the first TSP-like domain of METH2, amino acids 530 to 583 in SEQ ID NO:4; a polypeptide comprising the second TSP-like domain of METH2, amino acids 837 to 890 in SEQ ID NO:4; a polypeptide comprising amino acids 280 to 606 in SEQ ID NO:4; a polypeptide comprising amino acids 529 to 548 in SEQ ID NO:4; as well as polypeptides which are at least 95% identical, and more preferably at least 96%, 97%, 98% or 99% identical to the polypeptides described above and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a METH1 or METH2 polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the METH1 or METH2 polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in SEQ ID NO:2 or SEQ ID NO:4 or to the amino acid sequence encoded by deposited cDNA clones can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag *et al.*, *Comp. App. Biosci.* *6*:237-245 (1990). In a sequence alignment, the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number

of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total residues of the query sequence. Whether a residue is matched/aligned is determined by the results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a match/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched, the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time, the deletions are internal, so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case, the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of the present invention.

The polypeptides of the present invention are useful as a molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art.

In another aspect, the invention provides a peptide or polypeptide comprising an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion is an immunogenic or antigenic epitope of a polypeptide described herein. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA 81*:3998-4002 (1983).

As to the selection of peptides or polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G. *et al.*, "Antibodies that react with predetermined sites on proteins", *Science 219*:660-666 (1983). Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals.

Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson *et al.*, *Cell 37*:767-778 (1984) at 777.

Antigenic epitope-bearing peptides and polypeptides of the invention preferably contain a sequence of at least seven, more preferably at least nine and

most preferably between about at least about 15 to about 30 amino acids contained within the amino acid sequence of a polypeptide of the invention.

The epitope-bearing peptides and polypeptides of the invention may be produced by any conventional means. Houghten, R. A., "General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids", *Proc. Natl. Acad. Sci. USA 82*:5131-5135 (1985). This "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U.S. Patent No. 4,631,211 to Houghten *et al.* (1986).

As one of skill in the art will appreciate, METH1 or METH2 polypeptides of the present invention and the epitope-bearing fragments thereof described above can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life *in vivo*. This has been shown, e.g., for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins (EPA 394,827; Traunecker *et al., Nature 331*:84- 86 (1988)). Fusion proteins that have a disulfide-linked dimeric structure due to the IgG part can also be more efficient in binding and neutralizing other molecules than the monomeric METH1 or METH2 protein or protein fragment alone (Fountoulakis *et al., J. Biochem. 270*:3958-3964 (1995)).

METH1 and METH2 Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clones or shown in SEQ ID NO:1 or SEQ ID NO:3. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include

20 or more contiguous bases from the cDNA sequence contained in the deposited clones or the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:3. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of METH1 or METH2 polynucleotide fragments include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:1 or SEQ ID NO:3 or the cDNA contained in the deposited clones. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:2 or SEQ ID NO:4 or encoded by the cDNA contained in the deposited clones. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, or 281 to the end of the coding region or SEQ ID NO:2 or SEQ ID NO:4. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes

the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted METH1 or METH2 protein as well as the mature form. Further preferred polypeptide fragments include the secreted METH1 or METH2 protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted METH1 or METH2 polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted METH1 or METH2 protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these METH1 or METH2 polypeptide fragments are also preferred.

Particularly, N-terminal deletions of the METH1 polypeptide can be described by the general formula m-950, where m is an integer from 2 to 949, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:2. Preferably, N-terminal deletions of the METH1 polypeptide of the invention shown as SEQ ID NO:2 include polypeptides comprising the amino acid sequence of residues: G-2 to S-950; N-3 to S-950; A-4 to S-950; E-5 to S-950; R-6 to S-950; A-7 to S-950; P-8 to S-950; G-9 to S-950; S-10 to S-950; R-11 to S-950; S-12 to S-950; F-13 to S-950; G-14 to S-950; P-15 to S-950; V-16 to S-950; P-17 to S-950; T-18 to S-950; L-19 to S-950; L-20 to S-950; L-21 to S-950; L-22 to S-950; A-23 to S-950; A-24 to S-950; A-25 to S-950; L-26 to S-950; L-27 to S-950; A-28 to S-950; V-29 to S-950; S-30 to S-950; D-31 to S-950; A-32 to S-950; L-33 to S-950; G-34 to S-950; R-35 to S-950; P-36 to S-950; S-37 to S-950; E-38 to S-950; E-39 to S-950; D-40 to S-950; E-41 to S-950; E-42 to S-950; L-43 to S-950; V-44 to S-950; V-45 to S-950; P-46 to S-950; E-47 to S-950; L-48 to S-950; E-49 to S-950; R-50 to S-950; A-51 to S-950; P-52 to S-950; G-53 to S-950; H-54 to S-950; G-55 to S-950; T-56 to S-950; T-57 to S-950; R-58 to S-950; L-59 to S-950; R-60 to S-950; L-61 to S-950; H-62 to S-

950; A-63 to S-950; F-64 to S-950; D-65 to S-950; Q-66 to S-950; Q-67 to S-950; L-68 to S-950; D-69 to S-950; L-70 to S-950; E-71 to S-950; L-72 to S-950; R-73 to S-950; P-74 to S-950; D-75 to S-950; S-76 to S-950; S-77 to S-950; F-78 to S-950; L-79 to S-950; A-80 to S-950; P-81 to S-950; G-82 to S-950; F-83 to S-950; T-84 to S-950; L-85 to S-950; Q-86 to S-950; N-87 to S-950; V-88 to S-950; G-89 to S-950; R-90 to S-950; K-91 to S-950; S-92 to S-950; G-93 to S-950; S-94 to S-950; E-95 to S-950; T-96 to S-950; P-97 to S-950; L-98 to S-950; P-99 to S-950; E-100 to S-950; T-101 to S-950; D-102 to S-950; L-103 to S-950; A-104 to S-950; H-105 to S-950; C-106 to S-950; F-107 to S-950; Y-108 to S-950; S-109 to S-950; G-110 to S-950; T-111 to S-950; V-112 to S-950; N-113 to S-950; G-114 to S-950; D-115 to S-950; P-116 to S-950; S-117 to S-950; S-118 to S-950; A-119 to S-950; A-120 to S-950; A-121 to S-950; L-122 to S-950; S-123 to S-950; L-124 to S-950; C-125 to S-950; E-126 to S-950; G-127 to S-950; V-128 to S-950; R-129 to S-950; G-130 to S-950; A-131 to S-950; F-132 to S-950; Y-133 to S-950; L-134 to S-950; L-135 to S-950; G-136 to S-950; E-137 to S-950; A-138 to S-950; Y-139 to S-950; F-140 to S-950; I-141 to S-950; Q-142 to S-950; P-143 to S-950; L-144 to S-950; P-145 to S-950; A-146 to S-950; A-147 to S-950; S-148 to S-950; E-149 to S-950; R-150 to S-950; L-151 to S-950; A-152 to S-950; T-153 to S-950; A-154 to S-950; A-155 to S-950; P-156 to S-950; G-157 to S-950; E-158 to S-950; K-159 to S-950; P-160 to S-950; P-161 to S-950; A-162 to S-950; P-163 to S-950; L-164 to S-950; Q-165 to S-950; F-166 to S-950; H-167 to S-950; L-168 to S-950; L-169 to S-950; R-170 to S-950; R-171 to S-950; N-172 to S-950; R-173 to S-950; Q-174 to S-950; G-175 to S-950; D-176 to S-950; V-177 to S-950; G-178 to S-950; G-179 to S-950; T-180 to S-950; C-181 to S-950; G-182 to S-950; V-183 to S-950; V-184 to S-950; D-185 to S-950; D-186 to S-950; E-187 to S-950; P-188 to S-950; R-189 to S-950; P-190 to S-950; T-191 to S-950; G-192 to S-950; K-193 to S-950; A-194 to S-950; E-195 to S-950; T-196 to S-950; E-197 to S-950; D-198 to S-950; E-199 to S-950; D-200 to S-950; E-201 to S-950; G-202 to S-950; T-203 to S-950; E-204 to S-950; G-205 to S-950; E-206 to S-950; D-207 to S-950; E-

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Moreover, C-terminal deletions of the METH1 polypeptide can also be described by the general formula 1-n, where n is an integer from 2 to 950, where n corresponds to the position of amino acid residue identified in SEQ ID NO:2. Preferably, C-terminal deletions of the METH1 polypeptide of the invention shown as SEQ ID NO:2 include polypeptides comprising the amino acid sequence of residues: M-1 to C-949; M-1 to E-948; M-1 to A-947; M-1 to M-946; M-1 to T-945; M-1 to C-944; M-1 to F-943; M-1 to D-942; M-1 to I-941; M-1 to F-940; M-1 to H-939; M-1 to K-938; M-1 to P-937; M-1 to K-936; M-1 to K-935; M-1 to L-934; M-1 to P-933; M-1 to D-932; M-1 to C-931; M-1 to S-930; M-1 to E-929; M-1 to H-928; M-1 to S-927; M-1 to L-926; M-1 to V-925; M-1 to G-924; M-1 to G-923; M-1 to D-922; M-1 to H-921; M-1 to S-920; M-1 to L-919; M-1 to C-918; M-1 to K-917; M-1 to L-916; M-1 to S-915; M-1 to R-914; M-1 to K-913; M-1 to K-912; M-1 to Y-911; M-1 to G-910; M-1 to K-909; M-1 to G-908; M-1 to C-907; M-1 to T-906; M-1 to K-905; M-1 to S-904; M-1 to C-903; M-1 to S-902; M-1 to S-901; M-1 to W-900; M-1 to E-899; M-1 to G-898; M-1 to L-897; M-1 to Q-896; M-1 to W-895; M-1 to Q-894; M-1 to P-893; M-1 to C-892; M-1 to P-891; M-1 to H-890; M-1 to D-889; M-1 to A-888; M-1 to C-887; M-1 to P-886; M-1 to R-885; M-1 to T-884; M-1 to S-883; M-1 to A-882; M-1 to P-881; M-1 to K-880; M-1 to V-879; M-1 to E-878; M-1 to K-877; M-1 to A-876; M-1 to C-875; M-1 to E-874; M-1 to S-873; M-1 to A-872; M-1 to P-871; M-1 to Q-870; M-1 to G-869; M-1 to N-868; M-1 to I-867; M-1 to D-866; M-1 to R-865; M-1 to C-864; M-1 to E-863; M-1 to V-862; M-1 to L-861; M-1 to R-860; M-1 to R-859; M-1 to Q-858; M-1 to W-857; M-1 to G-856; M-1 to L-855; M-1 to E-854; M-1 to C-853; M-1 to S-852; M-1 to K-851; M-1 to S-850; M-1 to C-

849; M-1 to E-848; M-1 to G-847; M-1 to W-846; M-1 to E-845; M-1 to E-844; M-1 to I-843; M-1 to V-842; M-1 to W-841; M-1 to A-840; M-1 to S-839; M-1 to F-838; M-1 to T-837; M-1 to P-836; M-1 to I-835; M-1 to A-834; M-1 to N-833; M-1 to F-832; M-1 to S-831; M-1 to E-830; M-1 to K-829; M-1 to K-828; M-1 to K-827; M-1 to K-826; M-1 to V-825; M-1 to F-824; M-1 to Y-823; M-1 to T-822; M-1 to Y-821; M-1 to K-820; M-1 to I-819; M-1 to K-818; M-1 to P-817; M-1 to R-816; M-1 to L-815; M-1 to A-814; M-1 to N-813; M-1 to G-812; M-1 to V-811; M-1 to T-810; M-1 to L-809; M-1 to V-808; M-1 to Q-807; M-1 to I-806; M-1 to T-805; M-1 to L-804; M-1 to P-803; M-1 to E-802; M-1 to K-801; M-1 to L-800; M-1 to P-799; M-1 to S-798; M-1 to F-797; M-1 to S-796; M-1 to R-795; M-1 to I-794; M-1 to R-793; M-1 to E-792; M-1 to L-791; M-1 to A-790; M-1 to A-789; M-1 to S-788; M-1 to S-787; M-1 to G-786; M-1 to S-785; M-1 to Y-784; M-1 to R-783; M-1 to L-782; M-1 to V-781; M-1 to V-780; M-1 to G-779; M-1 to K-778; M-1 to Y-777; M-1 to M-776; M-1 to I-775; M-1 to D-774; M-1 to Q-773; M-1 to E-772; M-1 to L-771; M-1 to T-770; M-1 to S-769; M-1 to L-768; M-1 to T-767; M-1 to Y-766; M-1 to D-765; M-1 to G-764; M-1 to N-763; M-1 to L-762; M-1 to I-761; M-1 to Y-760; M-1 to T-759; M-1 to G-758; M-1 to D-757; M-1 to A-756; M-1 to A-755; M-1 to K-754; M-1 to I-753; M-1 to A-752; M-1 to L-751; M-1 to F-750; M-1 to S-749; M-1 to G-748; M-1 to N-747; M-1 to N-746; M-1 to R-745; M-1 to S-744; M-1 to G-743; M-1 to R-742; M-1 to Q-741; M-1 to N-740; M-1 to R-739; M-1 to Q-738; M-1 to K-737; M-1 to V-736; M-1 to E-735; M-1 to I-734; M-1 to N-733; M-1 to T-732; M-1 to A-731; M-1 to G-730; M-1 to T-729; M-1 to P-728; M-1 to I-727; M-1 to T-726; M-1 to I-725; M-1 to I-724; M-1 to D-723; M-1 to H-722; M-1 to Y-721; M-1 to G-720; M-1 to P-719; M-1 to K-718; M-1 to A-717; M-1 to S-716; M-1 to T-715; M-1 to V-714; M-1 to S-713; M-1 to G-712; M-1 to S-711; M-1 to I-710; M-1 to K-709; M-1 to K-708; M-1 to C-707; M-1 to T-706; M-1 to S-705; M-1 to G-704; M-1 to N-703; M-1 to G-702; M-1 to G-701; M-1 to C-700; M-1 to V-699; M-1 to G-698; M-1 to C-697; M-1 to K-696; M-1 to D-695; M-1 to F-694; M-1 to K-693; M-1 to K-692; M-1 to K-691; M-1 to S-690; M-1

to D-689; M-1 to I-688; M-1 to I-687; M-1 to R-686; M-1 to D-685; M-1 to C-684; M-1 to G-683; M-1 to A-682; M-1 to K-681; M-1 to V-680; M-1 to C-679; M-1 to Q-678; M-1 to G-677; M-1 to Q-676; M-1 to V-675; M-1 to C-674; M-1 to V-673; M-1 to S-672; M-1 to T-671; M-1 to S-670; M-1 to D-669; M-1 to P-668; M-1 to S-667; M-1 to C-666; M-1 to P-665; M-1 to T-664; M-1 to G-663; M-1 to D-662; M-1 to V-661; M-1 to V-660; M-1 to K-659; M-1 to P-658; M-1 to Q-657; M-1 to L-656; M-1 to V-655; M-1 to F-654; M-1 to F-653; M-1 to Y-652; M-1 to G-651; M-1 to I-650; M-1 to G-649; M-1 to K-648; M-1 to A-647; M-1 to Q-646; M-1 to C-645; M-1 to I-644; M-1 to L-643; M-1 to K-642; M-1 to C-641; M-1 to R-640; M-1 to D-639; M-1 to K-638; M-1 to P-637; M-1 to S-636; M-1 to V-635; M-1 to G-634; M-1 to A-633; M-1 to Y-632; M-1 to K-631; M-1 to P-630; M-1 to I-629; M-1 to W-628; M-1 to E-627; M-1 to V-626; M-1 to A-625; M-1 to P-624; M-1 to G-623; M-1 to S-622; M-1 to G-621; M-1 to F-620; M-1 to S-619; M-1 to A-618; M-1 to K-617; M-1 to S-616; M-1 to F-615; M-1 to E-614; M-1 to N-613; M-1 to H-612; M-1 to A-611; M-1 to E-610; M-1 to C-609; M-1 to Q-608; M-1 to E-607; M-1 to E-606; M-1 to R-605; M-1 to F-604; M-1 to T-603; M-1 to K-602; M-1 to G-601; M-1 to N-600; M-1 to N-599; M-1 to D-598; M-1 to P-597; M-1 to C-596; M-1 to D-595; M-1 to E-594; M-1 to L-593; M-1 to N-592; M-1 to C-591; M-1 to S-590; M-1 to R-589; M-1 to Y-588; M-1 to R-587; M-1 to V-586; M-1 to R-585; M-1 to K-584; M-1 to G-583; M-1 to E-582; M-1 to C-581; M-1 to Y-580; M-1 to K-579; M-1 to G-578; M-1 to G-577; M-1 to N-576; M-1 to K-575; M-1 to P-574; M-1 to V-573; M-1 to P-572; M-1 to N-571; M-1 to D-570; M-1 to C-569; M-1 to E-568; M-1 to R-567; M-1 to M-566; M-1 to T-565; M-1 to Y-564; M-1 to Q-563; M-1 to V-562; M-1 to G-561; M-1 to G-560; M-1 to G-559; M-1 to C-558; M-1 to T-557; M-1 to R-556; M-1 to S-555; M-1 to C-554; M-1 to D-553; M-1 to G-552; M-1 to W-551; M-1 to P-550; M-1 to G-549; M-1 to W-548; M-1 to M-547; M-1 to G-546; M-1 to W-545; M-1 to S-544; M-1 to G-543; M-1 to H-542; M-1 to F-541; M-1 to P-540; M-1 to T-539; M-1 to D-538; M-1 to F-537; M-1 to H-536; M-1 to K-535; M-1 to R-534; M-1 to D-533; M-1 to T-532; M-1 to K-531; M-1 to N-530;

M-1 to V-529; M-1 to C-528; M-1 to K-527; M-1 to G-526; M-1 to N-525; M-1 to I-524; M-1 to C-523; M-1 to W-522; M-1 to K-521; M-1 to G-520; M-1 to E-519; M-1 to G-518; M-1 to C-517; M-1 to S-516; M-1 to T-515; M-1 to G-514; M-1 to D-513; M-1 to A-512; M-1 to W-511; M-1 to P-510; M-1 to F-509; M-1 to H-508; M-1 to K-507; M-1 to T-506; M-1 to Q-505; M-1 to C-504; M-1 to V-503; M-1 to L-502; M-1 to V-501; M-1 to G-500; M-1 to G-499; M-1 to S-498; M-1 to T-497; M-1 to G-496; M-1 to T-495; M-1 to C-494; M-1 to W-493; M-1 to L-492; M-1 to T-491; M-1 to S-490; M-1 to C-489; M-1 to T-488; M-1 to S-487; M-1 to A-486; M-1 to A-485; M-1 to D-484; M-1 to P-483; M-1 to C-482; M-1 to H-481; M-1 to K-480; M-1 to S-479; M-1 to D-478; M-1 to E-477; M-1 to G-476; M-1 to F-475; M-1 to T-474; M-1 to F-473; M-1 to Q-472; M-1 to C-471; M-1 to Q-470; M-1 to R-469; M-1 to N-468; M-1 to A-467; M-1 to D-466; M-1 to Y-465; M-1 to S-464; M-1 to T-463; M-1 to G-462; M-1 to P-461; M-1 to L-460; M-1 to D-459; M-1 to G-458; M-1 to P-457; M-1 to L-456; M-1 to Q-455; M-1 to I-454; M-1 to P-453; M-1 to N-452; M-1 to Q-451; M-1 to P-450; M-1 to K-449; M-1 to D-448; M-1 to M-447; M-1 to L-446; M-1 to C-445; M-1 to E-444; M-1 to G-443; M-1 to H-442; M-1 to G-441; M-1 to N-440; M-1 to D-439; M-1 to L-438; M-1 to F-437; M-1 to S-436; M-1 to T-435; M-1 to I-434; M-1 to M-433; M-1 to Y-432; M-1 to A-431; M-1 to S-430; M-1 to C-429; M-1 to P-428; M-1 to S-427; M-1 to W-426; M-1 to P-425; M-1 to Q-424; M-1 to S-423; M-1 to H-422; M-1 to D-421; M-1 to L-420; M-1 to N-419; M-1 to S-418; M-1 to L-417; M-1 to M-416; M-1 to S-415; M-1 to A-414; M-1 to M-413; M-1 to M-412; M-1 to H-411; M-1 to S-410; M-1 to D-409; M-1 to Q-408; M-1 to N-407; M-1 to V-406; M-1 to G-405; M-1 to N-404; M-1 to L-403; M-1 to S-402; M-1 to A-401; M-1 to C-400; M-1 to Q-399; M-1 to K-398; M-1 to A-397; M-1 to D-396; M-1 to D-395; M-1 to H-394; M-1 to P-393; M-1 to M-392; M-1 to N-391; M-1 to F-390; M-1 to V-389; M-1 to H-388; M-1 to G-387; M-1 to L-386; M-1 to E-385; M-1 to H-384; M-1 to A-383; M-1 to T-382; M-1 to T-381; M-1 to F-380; M-1 to A-379; M-1 to A-378; M-1 to Q-377; M-1 to L-376; M-1 to G-375; M-1 to D-374; M-1 to D-373; M-1 to E-372; M-1 to I-371; M-1 to V-

370; M-1 to S-369; M-1 to C-368; M-1 to S-367; M-1 to R-366; M-1 to S-365; M-1 to P-364; M-1 to D-363; M-1 to C-362; M-1 to V-361; M-1 to T-360; M-1 to G-359; M-1 to V-358; M-1 to D-357; M-1 to A-356; M-1 to M-355; M-1 to G-354; M-1 to L-353; M-1 to T-352; M-1 to D-351; M-1 to C-350; M-1 to T-349; M-1 to Q-348; M-1 to S-347; M-1 to G-346; M-1 to C-345; M-1 to L-344; M-1 to D-343; M-1 to Q-342; M-1 to R-341; M-1 to T-340; M-1 to F-339; M-1 to L-338; M-1 to I-337; M-1 to A-336; M-1 to T-335; M-1 to D-334; M-1 to Y-333; M-1 to H-332; M-1 to E-331; M-1 to A-330; M-1 to D-329; M-1 to R-328; M-1 to D-327; M-1 to S-326; M-1 to P-325; M-1 to P-324; M-1 to N-323; M-1 to H-322; M-1 to Q-321; M-1 to K-320; M-1 to Q-319; M-1 to W-318; M-1 to N-317; M-1 to C-316; M-1 to F-315; M-1 to N-314; M-1 to R-313; M-1 to L-312; M-1 to T-311; M-1 to L-310; M-1 to A-309; M-1 to A-308; M-1 to N-307; M-1 to S-306; M-1 to T-305; M-1 to V-304; M-1 to E-303; M-1 to P-302; M-1 to G-301; M-1 to K-300; M-1 to Q-299; M-1 to E-298; M-1 to D-297; M-1 to H-296; M-1 to I-295; M-1 to V-294; M-1 to L-293; M-1 to I-292; M-1 to K-291; M-1 to V-290; M-1 to V-289; M-1 to V-288; M-1 to L-287; M-1 to S-286; M-1 to V-285; M-1 to S-284; M-1 to N-283; M-1 to R-282; M-1 to I-281; M-1 to S-280; M-1 to P-279; M-1 to H-278; M-1 to K-277; M-1 to Y-276; M-1 to L-275; M-1 to R-274; M-1 to A-273; M-1 to A-272; M-1 to V-271; M-1 to S-270; M-1 to F-269; M-1 to L-268; M-1 to T-267; M-1 to L-266; M-1 to L-265; M-1 to Y-264; M-1 to H-263; M-1 to K-262; M-1 to L-261; M-1 to G-260; M-1 to S-259; M-1 to G-258; M-1 to H-257; M-1 to F-256; M-1 to E-255; M-1 to A-254; M-1 to M-253; M-1 to S-252; M-1 to Q-251; M-1 to D-250; M-1 to A-249; M-1 to V-248; M-1 to L-247; M-1 to M-246; M-1 to T-245; M-1 to E-244; M-1 to V-243; M-1 to Y-242; M-1 to R-241; M-1 to H-240; M-1 to S-239; M-1 to S-238; M-1 to V-237; M-1 to F-236; M-1 to R-235; M-1 to K-234; M-1 to K-233; M-1 to R-232; M-1 to I-231; M-1 to S-230; M-1 to G-229; M-1 to T-228; M-1 to G-227; M-1 to T-226; M-1 to P-225; M-1 to Q-224; M-1 to G-223; M-1 to V-222; M-1 to G-221; M-1 to Q-220; M-1 to L-219; M-1 to A-218; M-1 to P-217; M-1 to D-216; M-1 to Q-215; M-1 to P-214; M-1 to S-213; M-1 to W-212; M-1 to

Q-211; M-1 to P-210; M-1 to G-209; M-1 to E-208; M-1 to D-207; M-1 to E-206; M-1 to G-205; M-1 to E-204; M-1 to T-203; M-1 to G-202; M-1 to E-201; M-1 to D-200; M-1 to E-199; M-1 to D-198; M-1 to E-197; M-1 to T-196; M-1 to E-195; M-1 to A-194; M-1 to K-193; M-1 to G-192; M-1 to T-191; M-1 to P-190; M-1 to R-189; M-1 to P-188; M-1 to E-187; M-1 to D-186; M-1 to D-185; M-1 to V-184; M-1 to V-183; M-1 to G-182; M-1 to C-181; M-1 to T-180; M-1 to G-179; M-1 to G-178; M-1 to V-177; M-1 to D-176; M-1 to G-175; M-1 to Q-174; M-1 to R-173; M-1 to N-172; M-1 to R-171; M-1 to R-170; M-1 to L-169; M-1 to L-168; M-1 to H-167; M-1 to F-166; M-1 to Q-165; M-1 to L-164; M-1 to P-163; M-1 to A-162; M-1 to P-161; M-1 to P-160; M-1 to K-159; M-1 to E-158; M-1 to G-157; M-1 to P-156; M-1 to A-155; M-1 to A-154; M-1 to T-153; M-1 to A-152; M-1 to L-151; M-1 to R-150; M-1 to E-149; M-1 to S-148; M-1 to A-147; M-1 to A-146; M-1 to P-145; M-1 to L-144; M-1 to P-143; M-1 to Q-142; M-1 to I-141; M-1 to F-140; M-1 to Y-139; M-1 to A-138; M-1 to E-137; M-1 to G-136; M-1 to L-135; M-1 to L-134; M-1 to Y-133; M-1 to F-132; M-1 to A-131; M-1 to G-130; M-1 to R-129; M-1 to V-128; M-1 to G-127; M-1 to E-126; M-1 to C-125; M-1 to L-124; M-1 to S-123; M-1 to L-122; M-1 to A-121; M-1 to A-120; M-1 to A-119; M-1 to S-118; M-1 to S-117; M-1 to P-116; M-1 to D-115; M-1 to G-114; M-1 to N-113; M-1 to V-112; M-1 to T-111; M-1 to G-110; M-1 to S-109; M-1 to Y-108; M-1 to F-107; M-1 to C-106; M-1 to H-105; M-1 to A-104; M-1 to L-103; M-1 to D-102; M-1 to T-101; M-1 to E-100; M-1 to P-99; M-1 to L-98; M-1 to P-97; M-1 to T-96; M-1 to E-95; M-1 to S-94; M-1 to G-93; M-1 to S-92; M-1 to K-91; M-1 to R-90; M-1 to G-89; M-1 to V-88; M-1 to N-87; M-1 to Q-86; M-1 to L-85; M-1 to T-84; M-1 to F-83; M-1 to G-82; M-1 to P-81; M-1 to A-80; M-1 to L-79; M-1 to F-78; M-1 to S-77; M-1 to S-76; M-1 to D-75; M-1 to P-74; M-1 to R-73; M-1 to L-72; M-1 to E-71; M-1 to L-70; M-1 to D-69; M-1 to L-68; M-1 to Q-67; M-1 to Q-66; M-1 to D-65; M-1 to F-64; M-1 to A-63; M-1 to H-62; M-1 to L-61; M-1 to R-60; M-1 to L-59; M-1 to R-58; M-1 to T-57; M-1 to T-56; M-1 to G-55; M-1 to H-54; M-1 to G-53; M-1 to P-52; M-1 to A-51; M-1 to R-50; M-1 to E-49; M-1 to L-48; M-1

to E-47; M-1 to P-46; M-1 to V-45; M-1 to V-44; M-1 to L-43; M-1 to E-42; M-1 to E-41; M-1 to D-40; M-1 to E-39; M-1 to E-38; M-1 to S-37; M-1 to P-36; M-1 to R-35; M-1 to G-34; M-1 to L-33; M-1 to A-32; M-1 to D-31; M-1 to S-30; M-1 to V-29; M-1 to A-28; M-1 to L-27; M-1 to L-26; M-1 to A-25; M-1 to A-24; M-1 to A-23; M-1 to L-22; M-1 to L-21; M-1 to L-20; M-1 to L-19; M-1 to T-18; M-1 to P-17; M-1 to V-16; M-1 to P-15; M-1 to G-14; M-1 to F-13; M-1 to S-12; M-1 to R-11; M-1 to S-10; M-1 to G-9; M-1 to P-8; M-1 to A-7; of SEQ ID NO:2. For example, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted METH1 polypeptide.

Moreover, N-terminal deletions of the METH2 polypeptide can be described by the general formula m-890, where m is an integer from 2 to 889, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:4. Preferably, N-terminal deletions of the METH2 polypeptide of the invention shown as SEQ ID NO:4 include polypeptides comprising the amino acid sequence of residues: F-2 to L-890; P-3 to L-890; A-4 to L-890; P-5 to L-890; A-6 to L-890; A-7 to L-890; P-8 to L-890; R-9 to L-890; W-10 to L-890; L-11 to L-890; P-12 to L-890; F-13 to L-890; L-14 to L-890; L-15 to L-890; L-16 to L-890; L-17 to L-890; L-18 to L-890; L-19 to L-890; L-20 to L-890; L-21 to L-890; L-22 to L-890; P-23 to L-890; L-24 to L-890; A-25 to L-890; R-26 to L-890; G-27 to L-890; A-28 to L-890; P-29 to L-890; A-30 to L-890; R-31 to L-890; P-32 to L-890; A-33 to L-890; A-34 to L-890; G-35 to L-890; G-36 to L-890; Q-37 to L-890; A-38 to L-890; S-39 to L-890; E-40 to L-890; L-41 to L-890; V-42 to L-890; V-43 to L-890; P-44 to L-890; T-45 to L-890; R-46 to L-890; L-47 to L-890; P-48 to L-890; G-49 to L-890; S-50 to L-890; A-51 to L-890; G-52 to L-890; E-53 to L-890; L-54 to L-890; A-55 to L-890; L-56 to L-890; H-57 to L-890; L-58 to L-890; S-59 to L-890; A-60 to L-890; F-61 to L-890; G-62 to L-890; K-63 to L-890; G-64 to L-890; F-65 to L-890; V-66 to L-890; L-67 to L-890; R-68 to L-890; L-69 to L-890; A-70 to L-890; P-71 to L-890; D-72 to L-890; D-73 to L-890; S-74 to L-890; F-75 to L-890; L-76 to L-890; A-77 to L-890; P-78 to L-890; E-79 to L-890; F-80 to L-890; K-81 to L-

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Moreover, C-terminal deletions of the METH2 polypeptide can also be described by the general formula 1-n, where n is an integer from 2 to 890 where n corresponds to the position of amino acid residue identified in SEQ ID NO:4. Preferably, C-terminal deletions of the METH2 polypeptide of the invention shown as SEQ ID NO:4 include polypeptides comprising the amino acid sequence of residues: M-1 to P-889; M-1 to C-888; M-1 to L-887; M-1 to Q-886; M-1 to S-885; M-1 to E-884; M-1 to C-883; M-1 to P-882; M-1 to K-881; M-1 to A-880; M-1 to D-879; M-1 to E-878; M-1 to P-877; M-1 to K-876; M-1 to L-875; M-1 to A-874; M-1 to K-873; M-1 to N-872; M-1 to C-871; M-1 to T-870; M-1 to A-869; M-1 to S-868; M-1 to A-867; M-1 to Q-866; M-1 to G-865; M-1 to S-

864; M-1 to P-863; M-1 to D-862; M-1 to R-861; M-1 to C-860; M-1 to E-859; M-1 to V-858; M-1 to T-857; M-1 to R-856; M-1 to R-855; M-1 to Q-854; M-1 to W-853; M-1 to G-852; M-1 to A-851; M-1 to G-850; M-1 to C-849; M-1 to T-848; M-1 to S-847; M-1 to S-846; M-1 to C-845; M-1 to E-844; M-1 to S-843; M-1 to W-842; M-1 to D-841; M-1 to G-840; M-1 to L-839; M-1 to V-838; M-1 to W-837; M-1 to Q-836; M-1 to A-835; M-1 to H-834; M-1 to L-833; M-1 to L-832; M-1 to P-831; M-1 to Q-830; M-1 to I-829; M-1 to I-828; M-1 to N-827; M-1 to T-826; M-1 to T-825; M-1 to A-824; M-1 to R-823; M-1 to E-822; M-1 to K-821; M-1 to S-820; M-1 to S-819; M-1 to Q-818; M-1 to M-817; M-1 to S-816; M-1 to F-815; M-1 to D-814; M-1 to V-813; M-1 to D-812; M-1 to N-811; M-1 to P-810; M-1 to V-809; M-1 to F-808; M-1 to F-807; M-1 to T-806; M-1 to Y-805; M-1 to K-804; M-1 to V-803; M-1 to K-802; M-1 to P-801; M-1 to P-800; M-1 to F-799; M-1 to V-798; M-1 to E-797; M-1 to G-796; M-1 to P-795; M-1 to V-794; M-1 to T-793; M-1 to L-792; M-1 to L-791; M-1 to Q-790; M-1 to V-789; M-1 to T-788; M-1 to L-787; M-1 to P-786; M-1 to E-785; M-1 to P-784; M-1 to L-783; M-1 to P-782; M-1 to R-781; M-1 to F-780; M-1 to S-779; M-1 to Q-778; M-1 to L-777; M-1 to R-776; M-1 to E-775; M-1 to L-774; M-1 to T-773; M-1 to A-772; M-1 to I-771; M-1 to S-770; M-1 to G-769; M-1 to S-768; M-1 to Y-767; M-1 to K-766; M-1 to L-765; M-1 to I-764; M-1 to T-763; M-1 to G-762; M-1 to K-761; M-1 to V-760; M-1 to L-759; M-1 to I-758; M-1 to D-757; M-1 to Q-756; M-1 to E-755; M-1 to I-754; M-1 to A-753; M-1 to S-752; M-1 to I-751; M-1 to A-750; M-1 to L-749; M-1 to N-748; M-1 to G-747; M-1 to N-746; M-1 to L-745; M-1 to L-744; M-1 to Y-743; M-1 to Q-742; M-1 to G-741; M-1 to D-740; M-1 to A-739; M-1 to T-738; M-1 to K-737; M-1 to L-736; M-1 to A-735; M-1 to L-734; M-1 to Y-733; M-1 to N-732; M-1 to G-731; M-1 to D-730; M-1 to N-729; M-1 to Q-728; M-1 to V-727; M-1 to G-726; M-1 to P-725; M-1 to H-724; M-1 to S-723; M-1 to R-722; M-1 to Q-721; M-1 to K-720; M-1 to V-719; M-1 to D-718; M-1 to I-717; M-1 to N-716; M-1 to T-715; M-1 to A-714; M-1 to G-713; M-1 to A-712; M-1 to P-711; M-1 to I-710; M-1 to T-709; M-1 to V-708; M-1 to I-707; M-1 to D-706; M-1 to N-705; M-1

to Y-704; M-1 to G-703; M-1 to Y-702; M-1 to N-701; M-1 to T-700; M-1 to P-699; M-1 to T-698; M-1 to L-697; M-1 to S-696; M-1 to G-695; M-1 to S-694; M-1 to V-693; M-1 to K-692; M-1 to R-691; M-1 to C-690; M-1 to S-689; M-1 to N-688; M-1 to G-687; M-1 to K-686; M-1 to G-685; M-1 to G-684; M-1 to C-683; M-1 to V-682; M-1 to G-681; M-1 to C-680; M-1 to K-679; M-1 to D-678; M-1 to L-677; M-1 to K-676; M-1 to R-675; M-1 to P-674; M-1 to S-673; M-1 to D-672; M-1 to V-671; M-1 to V-670; M-1 to H-669; M-1 to D-668; M-1 to C-667; M-1 to G-666; M-1 to A-665; M-1 to K-664; M-1 to V-663; M-1 to C-662; M-1 to Q-661; M-1 to G-660; M-1 to R-659; M-1 to V-658; M-1 to C-657; M-1 to I-656; M-1 to A-655; M-1 to L-654; M-1 to T-653; M-1 to E-652; M-1 to P-651; M-1 to G-650; M-1 to C-649; M-1 to L-648; M-1 to T-647; M-1 to G-646; M-1 to D-645; M-1 to I-644; M-1 to V-643; M-1 to K-642; M-1 to A-641; M-1 to E-640; M-1 to F-639; M-1 to V-638; M-1 to K-637; M-1 to F-636; M-1 to E-635; M-1 to S-634; M-1 to R-633; M-1 to G-632; M-1 to R-631; M-1 to A-630; M-1 to R-629; M-1 to C-628; M-1 to F-627; M-1 to L-626; M-1 to K-625; M-1 to C-624; M-1 to R-623; M-1 to D-622; M-1 to R-621; M-1 to P-620; M-1 to S-619; M-1 to V-618; M-1 to G-617; M-1 to A-616; M-1 to Y-615; M-1 to K-614; M-1 to P-613; M-1 to V-612; M-1 to W-611; M-1 to Q-610; M-1 to L-609; M-1 to L-608; M-1 to N-607; M-1 to G-606; M-1 to D-605; M-1 to M-604; M-1 to D-603; M-1 to T-602; M-1 to Y-601; M-1 to N-600; M-1 to Y-599; M-1 to A-598; M-1 to N-597; M-1 to Y-596; M-1 to K-595; M-1 to E-594; M-1 to C-593; M-1 to Q-592; M-1 to Q-591; M-1 to E-590; M-1 to R-589; M-1 to F-588; M-1 to S-587; M-1 to K-586; M-1 to G-585; M-1 to D-584; M-1 to P-583; M-1 to P-582; M-1 to C-581; M-1 to E-580; M-1 to E-579; M-1 to T-578; M-1 to H-577; M-1 to C-576; M-1 to S-575; M-1 to Q-574; M-1 to Y-573; M-1 to K-572; M-1 to A-571; M-1 to R-570; M-1 to R-569; M-1 to G-568; M-1 to L-567; M-1 to C-566; M-1 to Y-565; M-1 to R-564; M-1 to G-563; M-1 to G-562; M-1 to N-561; M-1 to Q-560; M-1 to P-559; M-1 to E-558; M-1 to P-557; M-1 to D-556; M-1 to K-555; M-1 to C-554; M-1 to E-553; M-1 to R-552; M-1 to H-551; M-1 to S-550; M-1 to F-549; M-1 to Q-548; M-1 to V-547; M-1 to G-546; M-1

to G-545; M-1 to G-544; M-1 to C-543; M-1 to T-542; M-1 to R-541; M-1 to S-540; M-1 to C-539; M-1 to E-538; M-1 to G-537; M-1 to W-536; M-1 to P-535; M-1 to G-534; M-1 to W-533; M-1 to P-532; M-1 to A-531; M-1 to W-530; M-1 to G-529; M-1 to G-528; M-1 to D-527; M-1 to V-526; M-1 to V-525; M-1 to P-524; M-1 to K-523; M-1 to P-522; M-1 to R-521; M-1 to E-520; M-1 to V-519; M-1 to E-518; M-1 to E-517; M-1 to E-516; M-1 to P-515; M-1 to L-514; M-1 to C-513; M-1 to S-512; M-1 to G-511; M-1 to E-510; M-1 to S-509; M-1 to C-508; M-1 to L-507; M-1 to H-506; M-1 to G-505; M-1 to P-504; M-1 to G-503; M-1 to C-502; M-1 to P-501; M-1 to T-500; M-1 to G-499; M-1 to D-498; M-1 to A-497; M-1 to W-496; M-1 to P-495; M-1 to L-494; M-1 to S-493; M-1 to G-492; M-1 to N-491; M-1 to K-490; M-1 to T-489; M-1 to H-488; M-1 to C-487; M-1 to L-486; M-1 to P-485; M-1 to E-484; M-1 to A-483; M-1 to G-482; M-1 to D-481; M-1 to T-480; M-1 to H-479; M-1 to C-478; M-1 to W-477; M-1 to L-476; M-1 to Q-475; M-1 to A-474; M-1 to C-473; M-1 to V-472; M-1 to D-471; M-1 to Q-470; M-1 to A-469; M-1 to S-468; M-1 to T-467; M-1 to N-466; M-1 to P-465; M-1 to C-464; M-1 to H-463; M-1 to R-462; M-1 to F-461; M-1 to D-460; M-1 to P-459; M-1 to G-458; M-1 to F-457; M-1 to I-456; M-1 to Q-455; M-1 to R-454; M-1 to C-453; M-1 to Q-452; M-1 to Q-451; M-1 to D-450; M-1 to L-449; M-1 to Q-448; M-1 to Y-447; M-1 to L-446; M-1 to A-445; M-1 to M-444; M-1 to R-443; M-1 to G-442; M-1 to P-441; M-1 to L-440; M-1 to G-439; M-1 to T-438; M-1 to P-437; M-1 to L-436; M-1 to P-435; M-1 to L-434; M-1 to A-433; M-1 to A-432; M-1 to G-431; M-1 to P-430; M-1 to A-429; M-1 to D-428; M-1 to L-427; M-1 to L-426; M-1 to C-425; M-1 to D-424; M-1 to G-423; M-1 to H-422; M-1 to G-421; M-1 to G-420; M-1 to D-419; M-1 to L-418; M-1 to L-417; M-1 to E-416; M-1 to T-415; M-1 to L-414; M-1 to Y-413; M-1 to M-412; M-1 to A-411; M-1 to S-410; M-1 to C-409; M-1 to P-408; M-1 to S-407; M-1 to W-406; M-1 to P-405; M-1 to L-404; M-1 to T-403; M-1 to Q-402; M-1 to N-401; M-1 to L-400; M-1 to H-399; M-1 to V-398; M-1 to F-397; M-1 to L-396; M-1 to P-395; M-1 to A-394; M-1 to M-393; M-1 to V-392; M-1 to H-391; M-1 to H-390; M-1 to K-389; M-1 to G-388; M-1 to M-387;

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1 to F-65; M-1 to G-64; M-1 to K-63; M-1 to G-62; M-1 to F-61; M-1 to A-60; M-1 to S-59; M-1 to L-58; M-1 to H-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to E-53; M-1 to G-52; M-1 to A-51; M-1 to S-50; M-1 to G-49; M-1 to P-48; M-1 to L-47; M-1 to R-46; M-1 to T-45; M-1 to P-44; M-1 to V-43; M-1 to V-42; M-1 to L-41; M-1 to E-40; M-1 to S-39; M-1 to A-38; M-1 to Q-37; M-1 to G-36; M-1 to G-35; M-1 to A-34; M-1 to A-33; M-1 to P-32; M-1 to R-31; M-1 to A-30; M-1 to P-29; M-1 to A-28; M-1 to G-27; M-1 to R-26; M-1 to A-25; M-1 to L-24; M-1 to P-23; M-1 to L-22; M-1 to L-21; M-1 to L-20; M-1 to L-19; M-1 to L-18; M-1 to L-17; M-1 to L-16; M-1 to L-15; M-1 to L-14; M-1 to F-13; M-1 to P-12; M-1 to L-11; M-1 to W-10; M-1 to R-9; M-1 to P-8; M-1 to A-7; of SEQ ID NO:4. Preferably, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted METH2 polypeptide.

The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:2 or SEQ ID NO:4, where n and m are integers as described above.

Also preferred are METH1 or METH2 polypeptide and polynucleotide fragments characterized by structural or functional domains. Preferred embodiments of the invention include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. As set out in the Figures, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha and beta amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions, and Jameson-Wolf high

antigenic index regions. Polypeptide fragments of SEQ ID NO:2 falling within conserved domains are specifically contemplated by the present invention. (See Figures 10 & 11 and Tables 1& 2.) Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active METH1 or METH2 fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the METH1 or METH2 polypeptide. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

However, many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:1 or SEQ ID NO:3 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 936 of SEQ ID NO:1, b is an integer of 15 to 950, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:1, and where the b is greater than or equal to a + 14. Moreover, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 876 of SEQ ID NO:3, b is an integer of 15 to 890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:3, and where the b is greater than or equal to a + 14.

Epitopes & Antibodies

In the present invention, "epitopes" refer to METH1 or METH2 polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates

to a METH1 or METH2 polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA 81*:3998-4002 (1983).)

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., *Proc. Natl. Acad. Sci. USA 82*:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson *et al.*, *Cell 37*:767-778 (1984); Sutcliffe, J. G. *et al.*, *Science 219*:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe *et al.*, supra; Wilson *et al.*, supra; Chow, M. *et al.*, *Proc. Natl. Acad. Sci. USA 82*:910-914; and Bittle, F. J. *et al.*, *J. Gen. Virol. 66*:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

Using DNAstar analysis, SEQ ID NO:2 was found antigenic at amino acids: 2-14, 32-44, 47-60, 66-78, 87-103, 109-118, 146-162, 168-180, 183-219, 223-243, 275-284, 296-306, 314-334, 341-354, 357-376, 392-399, 401-410, 418-429, 438-454, 456-471, 474-488, 510-522, 524-538, 550-561, 565-626, 630-643,

659-671, 679-721, 734-749, 784-804, 813-820, 825-832, 845-854, 860-894, 899-917, 919-924 and 928-939. Thus, these regions could be used as epitopes to produce antibodies against the protein encoded by METH1 cDNA.

Using DNAstar analysis, SEQ ID NO:4 was found antigenic at amino acids: 26-38, 45-52, 69-76, 80-99, 105-113, 129-136, 138-217, 254-263, 273-289, 294-313, 321-331, 339-356, 371-383, 417-427, 438-443, 459-471, 479-505, 507-526, 535-546, 550-607, 615-640, 648-653, 660-667, 669-681, 683-704, 717-732, 737-743, 775-787, 797-804, 811-825, 840-867 and 870-884. Thus, these regions could be used as epitopes to produce antibodies against the protein encoded by METH2 cDNA.

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')2 fragments) which are capable of specifically binding to protein. Fab and F(ab')2 fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl *et al.*, *J. Nucl. Med. 24*:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

Fusion Proteins

Any METH1 or METH2 polypeptide can be used to generate fusion proteins. For example, the METH1 or METH2 polypeptide, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the METH1 or METH2 polypeptide can be used to indirectly detect the second protein by binding to the METH1 or METH2. Moreover, because secreted proteins target cellular locations based on trafficking signals, the METH1 or METH2 polypeptides can be used as a targeting molecule once fused to other proteins.

Examples of domains that can be fused to METH1 or METH2 polypeptides include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the METH1 or METH2 polypeptide. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the METH1 or METH2 polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the METH1 or METH2 polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the METH1 or METH2 polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, METH1 or METH2 polypeptides, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker *et al.*, *Nature 331*:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.)

Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the METH1 or METH2 polypeptides can be fused to marker sequences, such as a peptide which facilitates purification of METH1 or METH2. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, *Proc. Natl. Acad. Sci. USA 86*:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the METH1 or METH2 polynucleotides or the polypeptides.

Biological Activities of METH1 or METH2

METH1 or METH2 polynucleotides and polypeptides can be used in assays to test for one or more biological activities. If METH1 or METH2 polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that METH1 or METH2 may be involved in the diseases associated with the biological activity. Therefore, METH1 or METH2 could be used to treat the associated disease.

Immune Activity

METH1 or METH2 polypeptides or polynucleotides may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, METH1 or METH2 polynucleotides or polypeptides can be used as a marker or detector of a particular immune system disease or disorder.

METH1 or METH2 polynucleotides or polypeptides may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. METH1 or METH2 polypeptides or polynucleotides could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, METH1 or METH2 polypeptides or polynucleotides can also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, METH1 or METH2 polynucleotides or polypeptides could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, METH1 or METH2 polynucleotides or polypeptides

that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting, important in the treatment of heart attacks (infarction), strokes, or scarring.

METH1 or METH2 polynucleotides or polypeptides may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of METH1 or METH2 polypeptides or polynucleotides that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by METH1 or METH2 include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by METH1 or METH2 polypeptides or polynucleotides. Moreover, METH1 or METH2 can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

METH1 or METH2 polynucleotides or polypeptides may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues.

The administration of METH1 or METH2 polypeptides or polynucleotides that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, METH1 or METH2 polypeptides or polynucleotides may also be used to modulate inflammation. For example, METH1 or METH2 polypeptides or polynucleotides may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

Hyperproliferative Disorders

METH1 or METH2 polypeptides or polynucleotides can be used to treat or detect hyperproliferative disorders, including neoplasms. METH1 or METH2 polypeptides or polynucleotides may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, METH1 or METH2 polypeptides or polynucleotides may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by METH1 or METH2 polynucleotides or polypeptides include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by METH1 or METH2 polynucleotides or polypeptides. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Infectious Disease

METH1 or METH2 polypeptides or polynucleotides can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, METH1 or METH2 polypeptides or polynucleotides may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by METH1 or METH2 polynucleotides or polypeptides. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g.,

Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox , hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. METH1 or METH2 polypeptides or polynucleotides can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by METH1 or METH2 polynucleotides or polypeptides include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema,

sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. METH1 or METH2 polypeptides or polynucleotides can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by METH1 or METH2 polynucleotides or polypeptides include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. METH1 or METH2 polypeptides or polynucleotides can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using METH1 or METH2 polypeptides or polynucleotides could either be by administering an effective amount of METH1 or METH2 polypeptide to the patient, or by removing cells from the patient, supplying the cells with METH1 or METH2 polynucleotide, and returning the engineered cells to the patient (*ex vivo* therapy). Moreover, the METH1 or METH2 polypeptide or polynucleotide can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

METH1 or METH2 polynucleotides or polypeptides can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, *Science 276*:59-87 (1997).) The regeneration of tissues could be used to

repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, METH1 or METH2 polynucleotides or polypeptides may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. METH1 or METH2 polynucleotides or polypeptides of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using METH1 or METH2 polynucleotides or polypeptides to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the METH1 or METH2 polynucleotides or polypeptides.

Chemotaxis

METH1 or METH2 polynucleotides or polypeptides may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

METH1 or METH2 polynucleotides or polypeptides may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. As a chemotactic molecule, METH1 or METH2 could also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that METH1 or METH2 polynucleotides or polypeptides may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, METH1 or METH2 polynucleotides or polypeptides could be used as an inhibitor of chemotaxis.

Binding Activity

METH1 or METH2 polypeptides may be used to screen for molecules that bind to METH1 or METH2 or for molecules to which METH1 or METH2 binds. The binding of METH1 or METH2 and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the METH1 or METH2 or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

Preferably, the molecule is closely related to the natural ligand of METH1 or METH2, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan *et al.*, *Current Protocols in*

Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which METH1 or METH2 binds, or at least, a fragment of the receptor capable of being bound by METH1 or METH2 (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express METH1 or METH2, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing METH1 or METH2(or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either METH1 or METH2 or the molecule.

The assay may simply test binding of a candidate compound toMETH1 or METH2, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to METH1 or METH2.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing METH1 or METH2, measuring METH1 or METH2/molecule activity or binding, and comparing the METH1 or METH2/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure METH1 or METH2 level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure METH1 or METH2 level or activity by either binding, directly or indirectly, to METH1 or METH2 or by competing with METH1 or METH2 for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to

bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the METH1 or METH2 molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of METH1 or METH2 from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to METH1 or METH2 comprising the steps of: (a) incubating a candidate binding compound with METH1 or METH2; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with METH1 or METH2, (b) assaying a biological activity , and (b) determining if a biological activity of METH1 or METH2 has been altered.

Other Activities

METH1 or METH2 polypeptides or polynucleotides may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

METH1 or METH2 polypeptides or polynucleotides may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, METH1 or METH2 polypeptides or polynucleotides may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

METH1 or METH2 polypeptides or polynucleotides may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

METH1 or METH2 polypeptides or polynucleotides may also be used as a food additive or preservative, such as to increase or decrease storage

capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Cancer Diagnosis and Prognosis

It is believed that certain tissues in mammals with cancer express significantly diminished levels of the METH1 or METH2 protein and mRNA encoding the METH1 or METH2 protein when compared to a corresponding "standard" mammal, i.e., a mammal of the same species not having the cancer. Further, it is believed that diminished levels of the METH1 or METH2 protein can be detected in certain body fluids (e.g., sera, plasma, urine, and spinal fluid) from mammals with cancer when compared to sera from mammals of the same species not having the cancer. Thus, the invention provides a diagnostic method useful during tumor diagnosis, which involves assaying the expression level of the gene encoding the METH1 protein in mammalian cells or body fluid and comparing the gene expression level with a standard METH1 gene expression level, whereby a decrease in the gene expression level under the standard is indicative of certain tumors. The invention also provides a diagnostic method useful during tumor diagnosis, which involves assaying the expression level of the gene encoding the METH2 protein in mammalian cells or body fluid and comparing the gene expression level with a standard METH2 gene expression level, whereby a decrease in the gene expression level under the standard is indicative of certain tumors.

Where a tumor diagnosis has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting diminished METH1 or METH2 gene expression will experience a worse clinical outcome relative to patients expressing the gene at a lower level.

(1990)), S1 nuclease mapping (Fujita *et al., Cell 49:*357- 367 (1987)), the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR) (Makino *et al., Technique 2:*295-301 (1990)), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

Assaying METH1 or METH2 protein levels in a biological sample can occur using antibody-based techniques. For example, METH1 or METH2 protein expression in tissues can be studied with classical immunohistological methods (Jalkanen, M., *et al., J. Cell. Biol. 101:*976-985 (1985); Jalkanen, M., *et al., J. Cell. Biol. 105:*3087-3096 (1987)).

Other antibody-based methods useful for detecting METH1 or METH2 protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA).

Suitable labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Modes of administration

It is recognized than an increase in the vascular supply plays a central role in tumor progression and metastasis; therefore, inhibitors of angiogenesis can prove effective as adjuvant therapy for cancer patients. Some of the currently recognized angiogenic suppressors are poor candidates for systemic treatment due to severe collateral effect. The present inventors have found that METH1 and METH2 are potent inhibitors of angiogenesis both *in vitro* and *in vivo*. The advantage of METH1 and METH1 is that these inhibitors are normally associated with suppression of physiological angiogenesis; therefore, they offer lack of toxicity and endothelial specificity over other angiogenic inhibitors. Furthermore,

METH1 and METH2 present a restricted pattern of expression providing a possible advantage on organ specificity.

Accordingly, the polypeptides of the present invention may be employed to treat cancer. The METH1 and METH2 polypeptides of the present invention can also be used to treat individuals with other disorders that are related to angiogenesis, including abnormal wound healing, inflammation, rheumatoid arthritis, psoriasis, endometrial bleeding disorders, diabetic retinopathy, some forms of macula degeneration, hemangiomas, and arterial-venous malformations.

Thus, the invention provides a method of inhibiting angiogenesis in an individual comprising administering to such an individual a pharmaceutical composition comprising an effective amount of an isolated METH1 polypeptide of the invention, effective to increase the METH1 activity level in such an individual. The invention also provides a method of inhibiting angiogenesis in an individual comprising administering to such an individual a pharmaceutical composition comprising an effective amount of an isolated METH2 polypeptide of the invention, effective to increase the METH2 activity level in such an individual.

METH1 polypeptides which may be used to inhibit angiogenesis in this manner include: METH1 polypeptide encoded by the deposited cDNA including the leader; the mature METH1 polypeptide encoded by the deposited the cDNA minus the leader (i.e., the mature protein); a polypeptide comprising amino acids about 1 to about 950 in SEQ ID NO:2; a polypeptide comprising amino acids about 2 to about 950 in SEQ ID NO:2; a polypeptide comprising amino acids about 29 to about 950 in SEQ ID NO:2; a polypeptide comprising amino acids about 30 to about 950 in SEQ ID NO:2; a polypeptide comprising the metalloprotease domain of METH1, amino acids 235 to 459 in SEQ ID NO:2; a polypeptide comprising the disintegrin domain of METH1, amino acids 460 to 544 in SEQ ID NO:2; a polypeptide comprising the first TSP-like domain of METH1, amino acids 545 to 598 in SEQ ID NO:2; a polypeptide comprising the second TSP-like domain of METH1, amino acids 841 to 894 in SEQ ID NO:2; a

polypeptide comprising the third TSP-like domain of METH1, amino acids 895 to 934 in SEQ ID NO:2; a polypeptide comprising amino acids 536 to 613 in SEQ ID NO:2; and a polypeptide comprising amino acids 549 to 563 in SEQ ID NO:2.

METH2 polypeptides which may be used to inhibit angiogenesis in this manner include: the METH2 polypeptide encoded by the deposited cDNA including the leader; the mature METH2 polypeptide encoded by the deposited the cDNA minus the leader (i.e., the mature protein); a polypeptide comprising amino acids about 1 to about 890 in SEQ ID NO:4; a polypeptide comprising amino acids about 2 to about 890 in SEQ ID NO:4; a polypeptide comprising amino acids about 24 to about 890 in SEQ ID NO:4; a polypeptide comprising amino acids about 112 to about 890 in SEQ ID NO:4; a polypeptide comprising the metalloprotease domain of METH2, amino acids 214 to 439 in SEQ ID NO:4; a polypeptide comprising the disintegrin domain of METH2, amino acids 440 to 529 in SEQ ID NO:4; a polypeptide comprising the first TSP-like domain of METH2, amino acids 530 to 583 in SEQ ID NO:4; a polypeptide comprising the second TSP-like domain of METH2, amino acids 837 to 890 in SEQ ID NO:4; a polypeptide comprising amino acids 280 to 606 in SEQ ID NO:4; and a polypeptide comprising amino acids 529 to 548 in SEQ ID NO:4.

As a general proposition, the total pharmaceutically effective amount of METH1 or METH2 polypeptide administered parenterally per dose will be in the range of about 1 μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the polypeptide. If given continuously, the METH1 or METH2 polypeptide is typically administered at a dose rate of about 1 μg/kg/hour to about 50 μg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed.

Pharmaceutical compositions containing the METH1 or METH2 of the invention may be administered orally, rectally, parenterally, intracistemally,

intravaginally, intraperitoneally, topically (as by powders, ointments, drops or transdermal patch), bucally, or as an oral or nasal spray. By "pharmaceutically acceptable carrier" is meant a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Chromosome Assays

The nucleic acid molecules of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. The mapping of DNAs to chromosomes according to the present invention is an important first step in correlating those sequences with genes associated with disease.

In certain preferred embodiments in this regard, the cDNA herein disclosed is used to clone genomic DNA of a METH1 or METH2 protein gene. This can be accomplished using a variety of well known techniques and libraries, which generally are available commercially. The genomic DNA then is used for *in situ* chromosome mapping using well known techniques for this purpose.

In addition, in some cases, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis of the 3' untranslated region of the gene is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes.

Fluorescence *in situ* hybridization ("FISH") of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with probes from the cDNA as

short as 50 or 60 bp. For a review of this technique, see Verma *et al.*, *Human Chromosomes: A Manual Of Basic Techniques*, Pergamon Press, New York (1988).

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in V. McKusick, *Mendelian Inheritance In Man*, available on-line through Johns Hopkins University, Welch Medical Library. The relationship between genes and diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (coinheritance of physically adjacent genes).

Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Identification and cloning of METH1 and METH2

To search for novel genes with TSP-like domains, a large human cDNA database consisting of approximately 900,00 expressed sequence tags (ESTs) was screened for sequences homologous to the second type I repeat of TSP1. Several ESTs were predicted to encode proteins with TSP-like domains. Two cDNA clones originated from human heart and lung libraries were further sequenced and chosen for functional analysis.

The amino-terminal end of METH1 was obtained using 5′ rapid amplification of cDNA ends (RACE) PCR technique (Marathon cDNA amplification kit, Clontech) according to manufacturer instructions. The amino-terminal end of METH2 was obtained partially through 5'RACE PCR and later confirmed and completed by genomic screening. For the genomic screen, BAC clones (Genome Systems) were initially identified by PCR. Positive BAC clones containing 150-200bp of sequence were subsequently subcloned into pGEM vector as small fragments and sequenced.

Analysis and comparison of the deduced amino acid sequence with the GenBank, EMBL and SwissProt databases suggested that these genes belong to a new family of metalloproteases with homology to the reprolysin family in their NH2-terminal end and with several TSP-like motifs in the COOH-terminal end. These cDNAs were named METH1 and METH2; ME, for metalloprotease and TH, for thrombospondin. The mouse homologue of METH1 was identified and named ADAMTS1 (Kuno, K., *et al., J. Biol. Chem. 272*:556-562 (1997)). Direct comparison of the human and mouse sequences revealed a high level of conservation (83.4% amino acid identity). Thus far no homologues for METH2 have been identified.

Interestingly, a recently identified protein named pNPI (procollagen I N-proteinase; (Colidge, A., *et al., Proc. Natl. Acad. Sci. USA 94*:2374-2379 (1997)) showed a striking sequence and structural similarity to METH1 and METH2 (Figure 3). As the novel proteins described here, pNPI also contains metalloproteinase (reprolysin subfamily) and TSP domains at the carboxy-terminal end. Although the sequence for pNPI is of bovine origin, sequence alignment revealed identical structural features. The amino acid similarity between METH1 and METH2 is 51.7%, and between METH1 or METH2 and pNPI the homology is lesser 33.9% and 36.3%, respectively.

Sequence analysis showed that the ORF of METH1 and METH2 coded for proteins of 950 and 890 amino acids, respectively. In all three proteins, the NH_2 terminal end contains a putative signal peptide followed by another putative

transmembrane domain around amino acid 300, deduced from the hydrophilicity plots. It is not clear whether these proteins are bound to the membrane. However, given preliminary data, it is more likely that this second transmembrane domain will consist of a hydrophobic pocket and that METH1, METH2 and pNPI are in fact secreted proteins. The NH_2-terminal end past the signal peptide has homology to the superfamily of zinc metalloproteases and can be subdivided in a prodomain, a metalloprotease domain, and a cysteine-rich region.

The double underlined sequence in METH1 and METH2 in Figure 3 localized at the boundary between the prodomain and the metalloprotease domain, are potential cleavage sites for mammalian subtilisins, such as furins (Barr, 1991). Proteolytical processing occurs in SVMPs to yield soluble metalloproteases and disintegrins (Bjarnason, J.B. & Fox, J.W., *Methods Enzymol. 248*:345-368 (1995)) and has also been detected in some ADAMs (reviewed by Wolsberg, T.G. & White, J.M., *Developmental Biology 180*:389-401 (1996)). At this point, preliminary experiments suggest that proteolytical processing occurs, at least in METH1. Additionally, both METH1 and METH2 present a Zn^{2+} -binding site (dotted line in Figure 3) that is presumed to be catalytically active due to the conservation of certain functionally important amino acids (Rawlings, N.D. & Barrett, A.J., *Methods Enzymol. 248*:183-228 (1995)) suggesting that these proteins may be active proteases. Following the metalloprotease domain, there is a cysteine-rich region which contains two putative disintegrin loops (Wolsberg, T.G. & White, J.M., *Developmental Biology 180*:389-401 (1996)) (marked by arrows in Figure 3). Disintegrin domains are found within the superfamily of metalloproteases in snake venom metalloproteases (SVMPs) and ADAMs (mammalian proteins containing a disintegrin and a metalloprotease domain) and have a possible function inhibiting binding of integrins to their ligands in SVMPs. Conversely, the ADAM-disintegrin-like domain, as part of membrane anchored proteins, may promote rather than disrupt, cell-cell interactions (Wolsberg, T.G. & White, J.M., *Developmental Biology 180*:389-401 (1996)). The TSP-like domains are located in the COOH-half of METH1 and METH2 proteins. METH1

contains two conserved TSP domains separated by a spacer region with unknown function, and a subdomain with less homology, and only 5 cysteines, following the second anti-angiogenic region. METH2 contains two TSP domains separated by the spacer region. The alignment of the TSP-like domains of METH1 and METH2 with those of TSP1 and TSP2 are shown in Figure 5. The homology varies between 19.2% to 52% amino acid similarity among all the TSP repeats. The cysteines, numbered 1 to 6, and the tryptophans, labeled by asterisks, are highly conserved.

Southern blot of human genomic DNA revealed the presence of METH1 and METH2 in the genome. METH1 and METH2 probes revealed bands of different size suggesting that they are transcribed from different genes.

The consensus sequence for the type I repeats includes 16 residues with 6 perfectly conserved cysteines. Typically it begins with the sequence motif WSXWS (SEQ ID NO:82) that has also been shown to bind to heparin (Guo, N., *et al., J. Biol. Chem. 267*:19349-19355 (1992)). The affinity of this region to heparin has been proposed to the part of the anti-angiogenic activity of TSP-1 (Guo, N., *et al., J. Peptide Res. 49* (1997)). Among the five members of the TSP family of proteins, only TSP-1 and TSP-2 inhibit angiogenesis and contain the type I repeats (Tolsma, S.S., *et al., J. Cell. Biol. 122*:497-511 (1993); Kyriakides, T.R., *et al., J. Cell Biol. 140*:419-430 (1998)). The type I or properdin repeats were probably added to the precursor of TSP1 and 2 by exon shuffling between 500 and 900 years ago (Adams, J., *et al., The Thrombospondin Gene Family*, 1 Ed. Molecular Biology Intelligence Unit (Springer, Ed.), R.G. Landes Company, Germany (1995)). It is likely that the acquisition of this domain provided the precursor of TSP1 and TSP2 with functions, such as regulation of new vessel formation. More recently, BAI-1 (brain angiogenic inhibitor-1), a protein isolated from a brain library for its ability to be regulated by p53, has also been shown to contain the type I repeat of TSP-1 and to provide anti-angiogenic potential to this molecule (Nishimori, H., *et al., Oncogene 15*:2145-2150 (1997)). Nevertheless, it appears that additional sequences or context are also important, since other

proteins containing the type I repeats appear not to have clear or more established anti-angiogenic properties such as: properdin, F-spondin, and other members of the complement family.

Because of the presence of TSP-repeats in METH1 and METH2, along with their anti-angiogenic properties, these proteins were originally considered members of the TSP superfamily. Nevertheless, they have no additional homology to other TSPs, and in fact, the similarity to TSP1 and TSP2 is restricted to the type I repeats. Furthermore, the proteins also have strong sequence and structural homology to members of the ADAM family. These features led Kuno and colleagues to name ADAMTS to the mouse homolog of METH1 (Kuno, K., *et al., J. Biol. Chem. 272*:556-562 (1997)). The recent identification of pNPI and its striking sequence homology to the proteins here described, prompt all these three proteins to be grouped in a subfamily named metallospondins. At this point, it is not clear whether pNIP has anti-angiogenic properties or whether METH1 and/or METH2 participate in the cleavage of the amino terminal pro-peptide of α1(I) procollagen.

Example 2: Northern and Southern blot analysis

Total RNA was purified from cells by guanidinium-isothiocyanate extraction, as previously described (Chomczynski, P. & Sacchi, N., *Anal. Biochem. 162*:156-159 (1987)) Poly(A)+RNA was extracted using a Boehringer Mannheim (BMB, Indianapolis, IN) kit according to the manufacturer conditions. Other poly(A)+RNA blots were purchased from Clontech (Palo Alto, CA). Pre-hybridization was performed in a solution containing: 50% formamide, 6X SSPE, 1X Denhardt's solution, 0.1% SDS and 100μg/ml of heat denatured salmon sperm DNA for 12-18h at 42°C. Hybridization with labeled cDNA probes proceeded in the same solution at 42°C for 12-18h. TSP1 and METH1 probes corresponded to the entire human cDNAs. METH2 probe corresponded to a *Kpn*I-*EcoR*I fragment from the human cDNA. A 1.3Kb *Pst*I fragment of the glyceraldehyde-3-

phosphate-dehydrogenase (GPDH) was used to normalize for loading and transfer efficiency. Membranes were exposed to Kodak Biomax MS film (Kodak, New Haven, CT).

For Southern blots, human genomic DNA, purchased from Promega (Madison, WI), was heated at 65°C for 10 min and digested with *Eco*RI and *Pst*I overnight at 37°C. 5µg of digested DNA was separated in a 1% agarose gel, transferred to a nytran membrane and cross-linked by ultraviolet light. cDNA probes, as well as, prehybridization and hybridization conditions were identical to those described for Northern blots. Blots were washed with high stringency (0.2X SSC, 0.2% SDS at 50°C).

The expression pattern of METH1 and METH2 was examined in both adult and embryonic tissues. Northern blot analysis was performed under high-stringency conditions with blots that included poly(A)+RNA from human tissues. METH1 and METH2 transcripts revealed a single band of 4.6 and 3.7Kb, respectively. Abundant METH1 mRNA expression was observed in adrenal, heart, placenta, followed by skeletal muscle, thyroid and stomach. From the embryonic tissues analyzed, kidney showed the highest expression of METH1 mRNA. Nevertheless, weaker expression of METH1 mRNA was seen in all tissues analyzed. Distribution of METH2 mRNA was more restricted and weaker than that of METH1. The highest expression was seen in lung, both embryonic and adult. Interestingly, METH1 and METH2 expression do not appear to overlap. In combination, the structural similarities and their pattern of expression suggest functional redundancy yet different transcriptional regulation. The expression levels of TSP1 transcripts in the same blots were also analyzed, for purpose of comparison. TSP1 mRNA highest expression was seen in the adult placenta and in all embryonic tissues analyzed. In contrast to METH1 and METH2 we observed constant levels of TSP1 transcript in all the other tissues examined.

The cell type distribution was also studied by Northern blot analysis of poly(A)+RNA. METH1 mRNA was detectable, at low levels, in dermal

fibroblasts, vascular smooth muscle, endometrial stromal cells, and in two cancer cell lines, HeLa and G631, an adenocarcinoma and a melanoma, respectively. METH2 mRNA was detected only on SW480, a colon carcinoma cell line, but no expression was seen in any other of the cell lines or primary strains analyzed.

The possibility that groups of angiogenic and anti-angiogenic factors regulate vascular network formation in specific organs has been a frequently discussed hypothesis likely to be true, yet unproven. The expression patterns of METH1 and METH2, which are clearly distinct and almost non-overlapping, were puzzling, at least with concern to overall levels. TSP1 and TSP2 also share identical structure, high level of amino acid similarity, yet their pattern of expression differs significantly (Iruela-Arispe, M.L., *Dev. Dyn. 197*:40-56 (1993)). The differences are likely based on dissimilar cis-acting elements in their promoters and different regulatory mechanisms, as previously suggested. Although the promoters for METH1 and 2 have not been characterized, it is likely that they provide unique features for the regulation of each gene. Nevertheless, the possibility that one motif, the anti-angiogenic / type I repeat, with demonstrated anti-angiogenic properties is present in several proteins with different tissue specificities is appealing. Alternatively, the small differences in sequence between closely related members of the same family could possess significance that goes beyond functional redundancy. In the case of TSP1 and TSP2, aside from the striking structural similarities and perhaps having functionally common anti-angiogenic properties, TSP1 and TSP2 also appear to display functions of their own and not likely shared by their similar relative. This became evident with the outcome of the two knock-outs for these genes. TSP1 null animals exhibited primarily lung disorders (Lawler, J., *et al., J. Clin. Invest. 101*:982-992 (1998)) and secondarily vascular abnormalities, but only under specific pathological settings or on a restricted set of organs. In contrast TSP2 knock-out mice exhibited unpredicted collagen assembly anomalies, with carry-on consequences to the skin, tendons, and bone (Kyriakides, T.R., *et al., J. Cell Biol. 140*:419-430 (1998)). In addition, these animals also appear to have overall

increase in capillary density in the dermis. It is not understood how the resemblance between the newly described members of the metallospondin family translate functionally. Clearly, pNIP has been shown to display active proteolytic activity by cleaving the N-terminus of type I procollagen (Colidge, A., *et al., Proc. Natl. Acad. Sci. USA 94*:2374-2379 (1997)).

A second region of functional interest corresponds to the disintegrin domain. This domain has been more fully characterized in related members of the snake venom metalloproteases that have been shown to bind to αIIbβ3 and inhibit platelet interaction blocking coagulation (Pfaff, M., *et al., Cell Adhes Commun. 2*:491-501 (1994); Usami, Y., *et al., Biochem. Biophys. Res. Commun. 201*:331-339 (1994)). The disintegrin motif consists of a thirteen to fifteen domain which frequently contain an RGD or a negatively charged residue at the position of the aspartic acid. The RGD, or equivalent, binds to integrins and serve as antagonist or signaling ligands (Wolsberg, T.G. & White, J.M., *Developmental Biology 180*:389-401 (1996)). METH2, but not METH1, has an RGD sequence located amino-terminal to the disintegrin domain. In addition, both molecules present relatively high, but not perfect, degree of conservation of cysteines within the disintegrin motif. This appears to display an important role in the tertiary structure of this region and its ability to interact with integrins. In addition, some of these domains have been shown to act as functional adhesion molecules, particularly those with transmembrane regions (Wolsberg, T.G. & White, J.M., *Developmental Biology 180*:389-401 (1996)). It is unlikely that this will be the case for METH1 and METH2, since both these proteins appear to be secreted.

Example 3: Expression and purification of recombinant proteins

Recombinant constructs for expression of truncated fusion proteins were as follows: (1) pRSET-METH1-Type I: METH1 nt 1605-1839 (from the start codon) was amplified by polymerase chain reaction using the following primers: 5′-GCA TTT TGG ATC CGC CTT TTC ATG-3′ (SEQ ID NO:78) and 5′-GTT

GTG TGC TGC AGA TTG TTC C-3′ (SEQ ID NO:79). The amplified fragment was then subcloned into the *Bam*HI and *Pst*I sites of the pRSET vector; (2) pGEX-METH1-TSP was generated by ligating the *Bam*HI-*Eco*RI fragment from the pRSET-METH1-TSP into the *Sma*I site of the pGEX-5X vector (Pharmacia Biotech Inc., Piscataway, NJ) by blunt-end ligation; (3) pGEX-1.0-METH2: the fragment nt 838-1818 of METH2 cDNA (from the start codon) was ligated into *Bam*HI-*Eco*RI sites of pGEM-2TK. The METH2 fragment was amplified by PCR using the following primers: 5′-GAAAAATGGGGATCCGAGGTG-3′ (SEQ ID NO:80) and 5′-GCAGGAGAATTCCGTCCATG-3′ (SEQ ID NO:81) to generate *Bam*HI and *Eco*RI restriction sites; (4) pGEX-METH2-TSP: a 0.5Kb *Xma*I-*Eco*RI fragment isolated from pGEX-1.0-METH2 was subcloned into the *Xma*I and *Eco*RI sites of pGEX-2TK vector. All constructs were sequenced to verify sequence fidelity and correct open reading frame.

The recombinant proteins were named 6H-METH1, the recombinant protein expressed with the plasmid pRSET-METH1-TSP, GST-METH1, the protein expressed with the plasmid pGEX-METH1-TSP and GST-METH2, the protein expressed with the plasmid pGEX-METH2-TSP.

Expression plasmids were transformed into BL21:DE3 *E. coli* strain (Stratagene Cloning Systems, La Jolla, CA) and fusion proteins were induced following manufacturer recommendations. Briefly, induced bacteria pellets were resuspended in PBS and sonicated on ice for 1 min. The suspension was, subsequently, incubated at RT for 20min in the presence of 1% triton X-100 and centrifuged at 4°C. Histidine tagged fusion proteins were then purified on Ni-NTA beads (Qiagen, Chatsworth, CA) by incubating 20ml of supernatant with 1ml of beads (50% slurry) for 2h at 4°C. The suspension was transferred into a column and washed with 10 columns volume of PBS containing 10mM imidazole, followed by 50mM imidazole and finally 100mM imidazole. The protein was eluted with 500mM imidazole in PBS. Fractions containing the recombinant protein were dialyzed against phenol-red free DMEM. Samples were centrifuged for 30min at 4°C, part of the protein was not soluble and was lost during

centrifugation. The supernatant was stored at -70°C and used for proliferation, cornea pocket and chorioallantoic membrane (CAM) assays.

For purification of GST-fusion proteins, the extract was cleared by centrifugation and applied to a GST-affinity column (Pharmacia). The column was washed with PBS-1% triton X-100 in the presence of 0.1mM reduced glutathione and, subsequently, with the same buffer in the presence of 0.5mM reduced glutathione. Fusion proteins were eluted with 10mM reduced glutathione in 50mM Tris-HCl, pH 7.5. Fractions containing the protein were dialyzed against DMEM, stored at -70°C and used for proliferation, cornea pocket and chorioallantoic membrane (CAM) assays.

Integrity and purity of recombinant proteins was analyzed in 12.5% or 15% acrylamide gels stained with Coomassie blue.

A recombinant GST fusion protein containing the first two type I repeats of TSP was also dialyzed against DMEM before used in functional assays. Intact TSP1 was purified from platelets as previously described (Roberts, D.D., *et al.*, *J. Tissue Cult. Methods 16*:217-222 (1994)).

To test the hypothesis that METH1 and METH2 TSP domains could function as regulators of angiogenesis recombinant fusion proteins were generated in bacteria. The constructs included the first TSP domain of METH1 or METH2. This domain is the most conserved, 52% amino acid similarity with the second type I repeat of TSP1, (this domain contains a putative binding site for CD36). All recombinant proteins were isolated under native conditions to preserve their secondary structure as much as possible. 6H-METH1 and GST-METH1 contained the first TSP-like domain of METH1 fused to a histidine tag or a GST, respectively. METH1 recombinant protein was made with two different tags because of purification and structural advantages. The differences in size are due to the size of the tag, 6KDa the histidine and 27KDa the GST. GST-METH2 contained the first TSP domain of METH2 also fused to a GST. A fragment corresponding to the last two type I repeats of TSP1, also fused to a GST, and

intact TSP1 purified from platelets were used as positive controls. In addition, GST alone was included in all experiments as negative control.

Example 4: TSP domains in METH1 and METH2 disrupt angiogenesis in vivo

Cornea pocket assay

Swiss Webster females and males, were purchased from Charles River (Boston, MA) and used between 8-10 weeks-old for implantation of the pellets. Cornea pockets were performed as described by Kenyon and colleagues (Kenyon, B.M., *et al., Invest. Ophthalmol. Vis. Sci. 37*:1625-1632 (1996)) with few modifications. Briefly, a solution of 10μg of recombinant bFGF plus 5 mg of sucralfate were mixed with 10μl of Hydron (200mg/ml in ethanol; New Brunswick, NJ) and the recombinant protein of interest (2μg). The suspension was then smeared onto a sterile nylon mesh square (pore size 500μm; Tetko Inc., Briarcliff Manor, NY) and allowed to dry for 30min. The fibers of the mesh were pulled to produce pellets of $500\mu m^3$ that were stored at -20°C. Uniformly sized pellets were selected under a microscope and used for the assays.

Mice were anesthetized with Avertin. An incision was made in the cornea using a Nikon SMZ-U dissecting microscope with the aid of a surgical blade. A single pellet was implanted into the pocket. Five days after pellet implantation, corneal angiogenesis was evaluated and photographed.

CAM assay

Chorioallantoic membrane assays were performed on Leghorn chicken embryos (SPAFAS, MA) at 12-14 days of embryonic development. Matrigel (750μg/ml), VEGF (250ng/mesh) and the protein or peptide to be tested were mixed, placed onto nylon meshes (pore size 250μm; Tetko Inc.) and incubated sequentially at 37°C for 30min and at 4°C for 2h to induce polymerization. A positive (matrigel and VEGF) and a negative (VEGF alone) control were also prepared for each CAM. Polymerized meshes were placed onto the third outer

region of the CAM and incubated for 24h. To visualize vessels, 400µl of fluorescein isothiocyanate dextran (10mg/ml, SIGMA) was injected in the chick blood stream. After 5-10min incubation, the chick was topically fixed with 3.7% formaldehyde for 5min. The meshes were then dissected and mounted onto slides. Fluorescence intensity was analyzed with a computer-assisted image program (NIH Image 1.59).

Peptides used on these assays were synthesized by Chiron (Raleigh, NC). Sequence corresponded to amino acids: P-TSP1, 430-447; P-METH1, 549-563; P-METH2, 529-548.

The evaluation of angiogenic or anti-angiogenic responses relies heavily on the sensitivity and specificity of the assays used to assess the response. To evaluate the anti-angiogenic activity of these fragments *in vivo*, two popular and well-accepted angiogenesis assays were used: the corneal pocket and the chorioallantoic membrane. The visibility, accessibility, and avascularity of the cornea are highly advantageous and facilitate the visualization of the neovascular response and the topical application of the test substances. A known amount of angiogenesis factor(s) is implanted, as a pellet, in a pocket made in the cornea eye. To test an angiogenesis inhibitor, the molecule is implanted with the stimulator in the same pellet, and the response is compared to the stimulator alone.

In these experiments, bFGF was used as the vascularization stimulator. Pellets containing the recombinant protein were implanted in mouse corneas and their ability to inhibit the bFGF-induced angiogenic response was compared to that of controls. When a bFGF pellet containing GST was implanted new capillary vessels grew from the cornea limbus, across the cornea and into the pellet within 5 days. In contrast, addition of GST-METH1 or GST-METH2 to the bFGF pellets completely abolished blood vessel growth. Table 4 contains a summary of the results obtained from 41 assays performed. Intact TSP1 purified from platelets and GST-TSP1 were used as positive controls. All assays were performed at identical concentrations, suggesting that METH1 and METH2 have similar potency to that of TSP1 in the inhibition of angiogenesis. In addition, when half

of the standard concentration was used, a weak, however noticeable response was seen, indicating a dose-dependent effect.

Table 4.
Activity of METH1 and METH2 recombinant proteins in the corneal pocket assay

bFGF Pellets	Vascularized corneas/Total corneas
Vehicle	5/5
TSP1	0/5
GST	11/11
GST-TSP1-TI	1/4
GST-METH1-TSP	0/8
GST-METH2-TSP	0/8

In the CAM assay, the angiogenic response is analyzed by measuring the number of vessels that grow within a matrix polymer containing the angiogenic growth factor. To determine whether recombinant METH1 and METH2 proteins inhibited neovascularization in the CAM assay induced by VEGF, a matrigel polymer containing VEGF and the recombinant protein were implanted in the CAM. Quantitative analysis of the experiments, which included three different polymers per treatment are shown in Figure 6A. Matrigels polymers containing VEGF plus 5μg of GST-METH1 or GST-METH2 caused greater than 80% inhibition in blood vessel growth. A similar potency was found using the GST recombinant protein derived from the type I repeats of TSP1. Furthermore, the anti-angiogenic effect of the TSP domains in METH1 and METH2 was dose-dependent with a complete inhibition of blood vessel growth when 15 μg/ml of protein was used (Figure 6C and D). GST alone, at identical concentrations, had no significant effect on VEGF-stimulated angiogenesis.

Synthetic peptides from the second or the third type I repeats of human TSP1 can mimic that anti-angiogenic effects of the intact TSP1 (Tolsma, S.S., *et al., J. Cell. Biol. 122*:497-511 (1993)). In fact, a 19-residue polypeptide was shown to be sufficient to block *in vivo* neovascularization in the rat cornea and to inhibit the bFGF-induced migration of cultured endothelial cells (Vogel, T., *et al., J. Cell. Biochem. 53*:74-84 (1993); Tolsma, S.S., *et al., J. Cell. Biol. 122*:497-511 (1993)). To test whether the same was true for the METH1 and METH2 TSP domains, peptides derived from the same region were synthesized and their anti-angiogenic activity was evaluated in the CAM assay. The results are shown in Figure 6B. Peptides derived from both the TSP domain of METH1 and METH2 blocked VEGF-induced angiogenesis similarly to that of TSP1. In contrast, scramble peptides had no significant effects.

Example 5: Proliferation assays

Human dermal endothelial cells (HDEC) were isolated and grown on Vitrogen™ coated petri-dishes in EBM (Clonetics, San Diego, CA) supplemented with 15% fetal calf serum, 25µg/ml cAMP, and 1µg/ml of hydrocortisone-21-acetate and were used from passages 3 to 6. Cells were made quiescent by incubation of confluent monolayers with phenol red-free EBM containing 0.2% BSA for 48h. Human dermal fibroblasts were isolated from neonatal foreskin and by enzymatic dissociation. Both fibroblasts and smooth muscle cells were maintained in DMEM supplemented with 10% fetal calf serum. Human mammary epithelial cells (HMEC) were purchased from Clonetics and maintained in the recommended media (mammary epithelial growth media, MEGM).

Quiescent human dermal endothelial cells, between passage 3 and 6, were plated on Vitrogen™ coated 24-well plates in EBM supplemented with 0.2% BSA, 0.1% fetal calf serum and 1 ng/ml of bFGF in the presence or absence of the recombinant protein and incubated at 5% CO_2 at 37°C for 48h. For vascular smooth muscle (VSM) and fibroblast proliferation assays, cells were incubated

under the same conditions but using DMEM instead of EBM. Human mammary epithelial cells were incubated on their growth media. A pulse of [^{3}H]-Thymidine (1μCi/μl) was added during the last 4h prior harvesting. Cells were washed and fixed in 10% TCA. Incorporation of [^{3}H]-thymidine was determined by scintillation counting, as previously described (Iruela-Arispe, M.L. & Sage, E.H., *J. Cell. Biochem. 52*:414 (1993)).

Statistical analysis were done using In-Stat software (Graph Pad Software) for Macintosh. Assuming normal distributions, data were analyzed by one-way ANOVA, followed by either T-test Dunnett test for comparisons between groups, or student-Newman-Kleus test for multiple comparisons between groups.

To gain insight into the mechanism by which METH1 and METH2 inhibit neovascularization, the direct effect of the purified recombinant fusion proteins on endothelial cell proliferation was tested. Serum-starved endothelial cells were plated into growth medium containing bFGF and FCS. Recombinant proteins (3μg/ml) were added at the same time of plating. 40% (GST-METH1), 45% (6H-GST) or 36% (GST-METH2) inhibition was observed, in contrast to a non-significant effect when GST alone was added. The recombinant protein from the type I repeats of TSP1 had similar inhibitory effects. (Figure 7A). Furthermore, suppression of proliferation mediated by METH1 or METH2 were dose-dependent, as shown in Figure 7E. The inhibition was observed as early as one day after treatment and the inhibitory effect was not toxic and reversible since the removal of the recombinant protein and subsequent addition of growth factor alone led to the resumption of endothelial cell proliferation.

The cell specificity of the anti-proliferative effects for METH1 and METH2 on the endothelium was evaluated by additional proliferation assays on a variety of non-endothelial cells. No significant inhibition of proliferation was seen on fibroblasts or smooth muscle cell cultures. In contrast, a non significant, but reproducible stimulation of proliferation for these two cell types could be observed. This result rules out the presence of any potential nonspecific inhibitor of cell growth in the recombinant protein preparations. On mammary epithelial

cell, however, METH1 and METH2 inhibited cell proliferation to the same degree as to endothelial cells. Interestingly, TSP1 also suppresses mammary epithelial cell proliferation both *in vitro* and in a transgenic model.

The possibility that METH1 and METH2 might act as disintegrins is consistent with their anti-angiogenic properties. Clearly blockade of $\alpha v\beta 3$ and $\beta 1$ integrins with antibodies has been shown to inhibit neovascularization both during development and in tumors (Brooks, P.C., *et al.*, *Cell 85*:683-693 (1996); Brooks, P.C., *et al.*, *Cell 92*:391-400 (1998); Senger, D.R., *et al.*, *Proc. Natl. Acad. Sci. USA 94*:13612-13617 (1997)). Integrins are essential for the mediation of both proliferative and migratory signals (Schwartz, M.A. & Ingber, D.E., *Mol. Biol. Cell 5*:389-393 (1994)), therefore interference with those signals can be highly deleterious to the angiogenic process. The angiogenic functional assays were performed with recombinant protein containing only the type I repeats in METH1 and METH2.

The mechanism of action of METH1 and METH2 with regards to their angio-inhibitory activity is not known. To date we have evidence that these proteins are secreted and bind to endothelial cells. Further investigations are guided towards the identification of receptors and signal transduction mechanisms. A likely hypothesis resulting from the lessons learned from TSP1 is that both METH1 and METH2 bind to CD36. Recently, this scavenger receptor has been implicated in the mediation of signals by which TSP-1 exert its anti-angiogenic effects (Dawson, D.W., *et al.*, *J. Cell. Biol. 138*:707-717 (1997)). Both the CSVTCG (SEQ ID NO:83) (Asch, A.S., *et al.*, *Nature 262*:1436-1439 (1993); Catimel, B., *et al.*, *Biochem. J. 284*:231-236 (1992)) and the GCQXR (SEQ ID NO:84) sequences have been proposed as primary binding motifs to CD36 (Dawson, D.W., *et al.*, *J. Cell. Biol. 138*:707-717 (1997)). METH1 and METH2 have almost entire conservation in both these regions. A complementary and also likely occurrence is binding of METH1 and METH2 to bFGF. Binding to heparin and bFGF has been proposed as part of the anti-angiogenic activity of TSP1 (Guo, N., *et al.*, *J. Peptide Res. 49* (1997)). This property appears to be mediated

through the WSXWS (SEQ ID NO:82) motif, also conserved in METH1 and METH2. Future efforts will focus on the signals implicated in the anti-angiogenic properties mediated by these novel proteins and on their potential as proteases of the extracellular milieu.

Example 6: Isolation of the METH1 or METH2 cDNA Clone From the Deposited Sample

Two approaches can be used to isolate METH1 or METH2 from the deposited sample. First, the deposited clone is transformed into a suitable host (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. A single colony is then used to generate DNA using nucleic acid isolation techniques well known to those skilled in the art. (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press.)

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:1 or SEQ ID NO:3 (i.e., within the region of SEQ ID NO:1 or SEQ ID NO:3 bounded by the 5' NT and the 3' NT of the clone) are synthesized and used to amplify the METH1 or METH2 cDNA using the deposited cDNA plasmids as templates. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 µg of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product

is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of the METH1 or METH2 gene which may not be present in the deposited clones. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine *et al.*, *Nucleic Acids Res. 21(7)*:1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the METH1 or METH2 gene of interest is used to PCR amplify the 5' portion of the METH1 or METH2 full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known

sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the METH1 or METH2 gene.

Example 7: Bacterial Expression of METH1 or METH2

A METH1 or METH2 polynucleotide encoding a METH1 or METH2 polypeptide invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 5, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites. The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final

concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified METH1 or METH2 protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the METH1 or METH2 protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified METH1 or METH2 protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a METH1 or METH2 polynucleotide, called pHE4a. (ATCC Accession Number 209645, deposited February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an *E. coli* origin

of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 5, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 8: Purification of METH1 or METH2 Polypeptide from an Inclusion Body

The following alternative method can be used to purify METH1 or METH2 polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The

homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 um membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the METH1 or METH2 polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring

of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant METH1 or METH2 polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Coomassie blue stained 16% SDS-PAGE gel when 5 ug of purified protein is loaded. The purified METH1 or METH2 protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 9: Cloning and Expression of METH1 or METH2 in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert METH1 or METH2 polynucleotide into a baculovirus to express METH1 or METH2. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned METH1 or METH2 polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the METH1 or METH2 cDNA sequence contained in the deposited clone, including the AUG initiation codon and any naturally associated leader sequence, is amplified using the PCR protocol described in Example 5. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0 ug of a commercially available linearized baculovirus DNA ("BaculoGold^{a} baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold^{a} virus DNA and 5 ug of the plasmid are mixed in a sterile

well of a microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27 degrees C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4 degree C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of ^{35}S-methionine and 5 uCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by

centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced METH1 or METH2 protein.

Example 10: Expression of METH1 or METH2 in Mammalian Cells

METH1 or METH2 polypeptide can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2DHFR (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, METH1 or METH2 polypeptide can be expressed in stable cell lines containing the METH1 or METH2 polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected METH1 or METH2 gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., *et al.*, *J. Biol. Chem. 253*:1357-1370 (1978); Hamlin, J. L. and Ma, C., *Biochem. et Biophys. Acta 1097*:107-143 (1990); Page, M. J. and Sydenham, M. A., *Biotechnology 9*:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy *et al.*, *Biochem J. 227*:277-279 (1991); Bebbington *et al.*, *Bio/Technology 10*:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-DHFR (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen *et al.*, *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart *et al.*, *Cell 41*:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of METH1 or METH2. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

If a naturally occurring signal sequence is used to produce a secreted protein, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence in an effort to secrete the protein from the cell. (See, e.g., WO 96/34891.)

The amplified fragment is then digested with the appropriate restriction enzyme and purified on a 1% agarose gel using a commercially available kit

("Geneclean," BIO 101 Inc., La Jolla, Ca.). The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 or pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 ug of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 uM, 2 uM, 5 uM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 uM. Expression of METH1 or METH2 is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 11: Construction of N-Terminal and/or C-Terminal Deletion Mutants

The following general approach may be used to clone a N-terminal or C-terminal deletion METH1 or METH2 deletion mutant. Generally, two oligonucleotide primers of about 15-25 nucleotides are derived from the desired 5' and 3' positions of a polynucleotide of SEQ ID NO:1 or SEQ ID NO:3. The 5' and 3' positions of the primers are determined based on the desired METH1 or

METH2 polynucleotide fragment. An initiation and stop codon are added to the 5' and 3' primers respectively, if necessary, to express the METH1 or METH2 polypeptide fragment encoded by the polynucleotide fragment. Preferred METH1 or METH2 polynucleotide fragments are those encoding the N-terminal and C-terminal deletion mutants disclosed above in the "Polynucleotide and Polypeptide Fragments" section of the Specification.

Additional nucleotides containing restriction sites to facilitate cloning of the METH1 or METH2 polynucleotide fragment in a desired vector may also be added to the 5' and 3' primer sequences. The METH1 or METH2 polynucleotide fragment is amplified from genomic DNA or from the deposited cDNA clone using the appropriate PCR oligonucleotide primers and conditions discussed herein or known in the art. The METH1 or METH2 polypeptide fragments encoded by the METH1 or METH2 polynucleotide fragments of the present invention may be expressed and purified in the same general manner as the full length polypeptides, although routine modifications may be necessary due to the differences in chemical and physical properties between a particular fragment and full length polypeptide.

As a means of exemplifying but not limiting the present invention, the polynucleotide encoding the METH1 polypeptide fragment D-40 to S-950 or the METH2 polypeptide fragment L-20 to L-890 is amplified and cloned as follows: A 5' primer is generated comprising a restriction enzyme site followed by an initiation codon in frame with the polynucleotide sequence encoding the N-terminal portion of the polypeptide fragment beginning with D-40 or L-20, respectively. A complementary 3' primer is generated comprising a restriction enzyme site followed by a stop codon in frame with the polynucleotide sequence encoding C-terminal portion of the METH1 or METH2 polypeptide fragment ending with S-950 or L-890, respectively.

The amplified polynucleotide fragment and the expression vector are digested with restriction enzymes which recognize the sites in the primers. The digested polynucleotides are then ligated together. The METH1 or METH2

polynucleotide fragment is inserted into the restricted expression vector, preferably in a manner which places the METH1 or METH2 polypeptide fragment coding region downstream from the promoter. The ligation mixture is transformed into competent *E. coli* cells using standard procedures and as described in the Examples herein. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Example 12: Protein Fusions of METH1 or METH2

METH1 or METH2 polypeptides are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of METH1 or METH2 polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 7; see also EP A 394,827; Traunecker, *et al.*, *Nature 331*:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to METH1 or METH2 polypeptides can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 7.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site

should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and METH1 or METH2 polynucleotide, isolated by the PCR protocol described in Example 5, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCC
CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGT
CACATGCGTGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAA
AGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGT
CCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAG
TGCAAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCA
TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACC
TGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT
GCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGG
ACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTG
TCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:85)

Example 13: Production of an Antibody

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing METH1 or METH2 is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of METH1 or METH2 protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Kohler *et al.*, *Nature 256*:495 (1975); Kohler *et al.*, *Eur. J. Immunol. 6*:511 (1976); Kohler *et al.*, *Eur. J. Immunol. 6*:292 (1976); Hammerling *et al.*, in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with METH1 or METH2 polypeptide or, more preferably, with a secreted METH1 or METH2 polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degree C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands *et al.* (*Gastroenterology 80*:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify

clones which secrete antibodies capable of binding the METH1 or METH2 polypeptide.

Alternatively, additional antibodies capable of binding to METH1 or METH2 polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the METH1 or METH2 protein-specific antibody can be blocked by METH1 or METH2. Such antibodies comprise anti-idiotypic antibodies to the METH1 or METH2 protein-specific antibody and can be used to immunize an animal to induce formation of further METH1 or METH2 protein-specific antibodies.

It will be appreciated that Fab and F(ab')2 and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). Alternatively, secreted METH1 or METH2 protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, *Science 229*:1202 (1985); Oi *et al.*, *BioTechniques 4*:214 (1986); Cabilly *et al.*, U.S. Patent No. 4,816,567; Taniguchi *et al.*, EP 171496; Morrison *et al.*, EP 173494; Neuberger *et al.*, WO 8601533; Robinson *et al.*, WO 8702671; Boulianne *et al.*, *Nature 312*:643 (1984); Neuberger *et al.*, *Nature 314*:268 (1985).)

Example 14: Production Of METH1 or METH2 Protein For High-Throughput Screening Assays

The following protocol produces a supernatant containing METH1 or METH2 polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 16-23.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 10-12, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not

spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of $CaCl_2$ (anhyd); 0.00130 mg/L $CuSO_4$-$5H_2O$; 0.050 mg/L of $Fe(NO_3)_3$-$9H_2O$; 0.417 mg/L of $FeSO_4$-$7H_2O$; 311.80 mg/L of Kcl; 28.64 mg/L of $MgCl_2$; 48.84 mg/L of $MgSO_4$; 6995.50 mg/L of NaCl; 2400.0 mg/L of $NaHCO_3$; 62.50 mg/L of NaH_2PO_4-H_20; 71.02 mg/L of Na_2HPO_4; .4320 mg/L of $ZnSO_4$-$7H_2O$; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H_20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H_20; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H_20; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-$2H_20$; and 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B_{12}; 25 mM of HEPES Buffer; 2.39 mg/L of

Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 16-23.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the METH1 or METH2 polypeptide directly (e.g., as a secreted protein) or by METH1 or METH2 inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 15: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the

Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, *Ann. Rev. Biochem.* *64*:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proxial region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:82)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	JAKs				STATS	GAS(elements) or ISRE
Ligand	tyk2	Jak1	Jak2	Jak3		
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotrophic)	?	+	?	?	1,3	
OnM(Pleiotrophic)	?	+	+	?	1,3	
LIF(Pleiotrophic)	?	+	+	?	1,3	
CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrophic)	?	+	?	?	1,3	
IL-12(Pleiotrophic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	GAS(B-CAS>IRF1=IFP>>Ly6)
EPO	?	-	+	-	5	
Receptor Tyrosine Kinases						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	GAS (not IRF1)
CSF-1	?	+	+	-	1,3	

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 16-17, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman *et al.*, *Immunity 1*:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:86)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:87)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:88)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter

molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 16-17.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 18 and 19. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 16: High-Throughput Screening Assay for T-cell Activity

The following protocol is used to assess T-cell activity of METH1 or METH2 by determining whether METH1 or METH2 supernatant proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 15. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing METH1 or METH2 polypeptides or METH1 or METH2 induced polypeptides as produced by the protocol described in Example 14.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 20. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

Example 17: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity of METH1 or METH2 by determining whether METH1 or METH2 proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 15. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 15, a DEAE-Dextran method (Kharbanda *et. al.*, 1994, *Cell Growth & Differentiation* 5:259-265) is used. First, harvest $2x10e^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4 \cdot 7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37 degree C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 14. Incubate at 37 degee C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 20.

Example 18: High-Throughput Screening Assay Identifying Neuronal Activity

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by METH1 or METH2.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by METH1 or METH2 can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K *et al.*, *Oncogene* 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:89)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:90)

Using the GAS:SEAP/Neo vector produced in Example 15, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 14. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add 50 ul supernatant produced by Example 14, 37 degree

C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 20.

Example 19: High-Throughput Screening Assay for T-cell Activity

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 14. Activators or inhibitors of NF-KB would be useful in treating diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:91), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCG
GGACTTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:92)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:93)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACT
TTCCATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAA
CTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCG
CCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGC
CTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGA
GGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:88)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 16. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 16. As a positive control, exogenous TNF alpha (0.1,1,

10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 20: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 16-19, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5

19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 21: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to

detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50 ul of 12 ug/ml fluo-3 is added to each well. The plate is incubated at 37 degree C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degree C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-3. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates

an extracellular signaling event caused by the a molecule, either METH1 or METH2 or a molecule induced by METH1 or METH2, which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 22: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether METH1 or METH2 or a molecule induced by METH1 or METH2 is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses

with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 14, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg^{2+} (5mM ATP/50mM MgCl2), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 23: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 22, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 14 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place

of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard

procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by METH1 or METH2 or a molecule induced by METH1 or METH2.

Example 24: Method of Determining Alterations in the METH1 or METH2 Gene

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:1. Suggested PCR conditions consist of 35 cycles at 95 degree C for 30 seconds; 60-120 seconds at 52-58 degree C; and 60-120 seconds at 70 degree C, using buffer solutions described in Sidransky, D. *et al.*, *Science 252*:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons of METH1 or METH2 is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations in METH1 or METH2 is then cloned and sequenced to validate the results of the direct sequencing.

PCR products of METH1 or METH2 are cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., *Nucleic Acids Research 19*:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations in METH1 or METH2 not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in the METH1 or METH2 gene. Isolated genomic clones are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim),

and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the METH1 or METH2 genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. *et al.*, *Genet. Anal. Tech. Appl. 8*:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region of METH1 or METH2 (hybridized by the probe) are identified as insertions, deletions, and translocations. These METH1 or METH2 alterations are used as a diagnostic marker for an associated disease.

Example 25: Method of Detecting Abnormal Levels of METH1 or METH2 in a Biological Sample

METH1 or METH2 polypeptides can be detected in a biological sample, and if an increased or decreased level of METH1 or METH2 is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect METH1 or METH2 in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies to METH1 or METH2, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 13. The wells are blocked so that non-specific binding of METH1 or METH2 to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing METH1 or METH2. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded METH1 or METH2.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot METH1 or METH2 polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the METH1 or METH2 in the sample using the standard curve.

Example 26: Formulating a Polypeptide

The METH1 or METH2 composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the METH1 or METH2 polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of METH1 or METH2 administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and

1 mg/kg/day for the hormone. If given continuously, METH1 or METH2 is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing METH1 or METH2 are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

METH1 or METH2 is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. *et al.*, *Biopolymers 22*:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer *et al.*, *J. Biomed. Mater. Res. 15*:167-277 (1981), and R. Langer, *Chem. Tech. 12*:98-105 (1982)), ethylene vinyl acetate (R. Langer *et al.*) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped METH1 or METH2 polypeptides. Liposomes containing the METH1 or METH2 are prepared by methods known per se: DE 3,218,121; Epstein *et al.*, *Proc. Natl. Acad. Sci. USA 82*:3688-3692 (1985); Hwang *et al.*, *Proc. Natl. Acad. Sci. USA 77*:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324.

Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, METH1 or METH2 is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting METH1 or METH2 uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as

EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

METH1 or METH2 is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

METH1 or METH2 used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

METH1 or METH2 polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous METH1 or METH2 polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized METH1 or METH2 polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, METH1 or METH2 may be employed in conjunction with other therapeutic compounds.

Example 27: Method of Treating Decreased Levels of METH1 or METH2

The present invention relates to a method for treating an individual in need of a decreased level of METH1 or METH2 activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of METH1 or METH2 antagonist. Preferred antagonists for use in the present invention are METH1 or METH2-specific antibodies.

Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of METH1 or METH2 in an individual can be treated by administering METH1 or METH2, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of METH1 or METH2 polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of METH1 or METH2 to increase the activity level of METH1 or METH2 in such an individual.

For example, a patient with decreased levels of METH1 or METH2 polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 26.

Example 28: Method of Treating Increased Levels of METH1 or METH2

The present invention also relates to a method for treating an individual in need of an increased level of METH1 or METH2 activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of METH1 or METH2 or an agonist thereof.

Antisense technology is used to inhibit production of METH1 or METH2. This technology is one example of a method of decreasing levels of METH1 or METH2 polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of METH1 or METH2 is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 26.

Example 29: Method of Treatment Using Gene Therapy - Ex Vivo

One method of gene therapy transplants fibroblasts, which are capable of expressing METH1 or METH2 polypeptides, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. *et al.*, *DNA 7*:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding METH1 or METH2 can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 5. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus

linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector contains properly inserted METH1 or METH2.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the METH1 or METH2 gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the METH1 or METH2 gene(the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether METH1 or METH2 protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 30: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) METH1 or METH2 sequences into an animal to increase or decrease the expression of the METH1 or METH2 polypeptide. The METH1 or METH2 polynucleotide may be operatively linked to a promoter or any other genetic elements necessary for the expression of the METH1 or METH2 polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. *et al.* (1997) *Cardiovasc. Res. 35(3)*:470-479, Chao, J *et al.* (1997) *Pharmacol. Res. 35(6)*:517-522, Wolff J.A. (1997) *Neuromuscul. Disord. 7(5)*:314-318, Schwartz, B. *et al.* (1996) *Gene Ther. 3(5)*:405-411, Tsurumi Y. *et al.* (1996) *Circulation 94(12)*:3281-3290 (incorporated herein by reference).

The METH1 or METH2 polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The METH1 or METH2 polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the METH1 or METH2 polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. *et al.* (1995) *Ann. NY Acad. Sci. 772*:126-139 and Abdallah B. *et al.* (1995) *Biol. Cell 85(1)*:1-7) which can be prepared by methods well known to those skilled in the art.

The METH1 or METH2 polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The METH1 or METH2 polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked METH1 or METH2 polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about

0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked METH1 or METH2 polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected METH1 or METH2 polynucleotide in muscle *in vivo* is determined as follows. Suitable METH1 or METH2 template DNA for production of mRNA coding for METH1 or METH2 polypeptide is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The METH1 or METH2 template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for METH1 or METH2 protein expression. A time course for METH1 or METH2 protein expression may

be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of METH1 or METH2 DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using METH1 or METH2 naked DNA.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference.

Applicant's or agent's file reference number: 1488.107PC02	International application No: TBA

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 32, lines 16-17.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depository institution

American Type Culture Collection

Address of depository institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

formerly at: 12301 Parklawn Drive
Rockville, Maryland 20852
United States of America

Date of deposit	Accession Number
15 January 1998	209581

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

DNA plasmid HOUCQ17

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications, e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

Applicant's or agent's file reference number: 1488.107PC02	International application No: TBA

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 32, lines 25-26.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depository institution

American Type Culture Collection

Address of depository institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

formerly at: 12301 Parklawn Drive
Rockville, Maryland 20852
United States of America

Date of deposit	Accession Number
15 January 1998	209582

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

DNA plasmid HCE4D69

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications, e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding a polypeptide comprising amino acids 1 to 950 in SEQ ID NO:2;

(b) a polynucleotide encoding a polypeptide comprising amino acids 2 to 950 in SEQ ID NO:2;

(c) a polynucleotide encoding a polypeptide comprising amino acids 29 to 950 in SEQ ID NO:2;

(d) a polynucleotide encoding a polypeptide comprising amino acids 30 to 950 in SEQ ID NO:2;

(e) a polynucleotide comprising a nucleotide sequence encoding the METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(f) a polynucleotide comprising a nucleotide sequence encoding the mature METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(g) a polynucleotide encoding a polypeptide comprising amino acids 1 to 890 in SEQ ID NO:4;

(h) a polynucleotide encoding a polypeptide comprising amino acids 2 to 890 in SEQ ID NO:4;

(i) a polynucleotide encoding a polypeptide comprising amino acids 24 to 890 in SEQ ID NO:4;

(j) a polynucleotide encoding a polypeptide comprising amino acids 112 to 890 in SEQ ID NO:4;

(k) a polynucleotide comprising a nucleotide sequence encoding the METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582;

(l) a polynucleotide comprising a nucleotide sequence encoding the mature METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582;

(m) a polynucleotide variant created by altering a polynucleotide of (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), or (l), wherein:

(i) said altering includes a nucleotide insertion, deletion, or substitution, or any combination thereof; and

(ii) the number of alterations is equal to or less than 5% of the total number of nucleotides present in the unaltered polynucleotide;

(n) a polynucleotide encoding amino acids 235 to 459 in SEQ ID NO:2;

(o) a polynucleotide encoding amino acids 460 to 544 in SEQ ID NO:2;

(p) a polynucleotide encoding amino acids 545 to 598 in SEQ ID NO:2;

(q) a polynucleotide encoding amino acids 841 to 894 in SEQ ID NO:2;

(r) a polynucleotide encoding amino acids 895 to 934 in SEQ ID NO:2;

(s) a polynucleotide encoding amino acids 536 to 613 in SEQ ID NO:2;

(t) a polynucleotide encoding amino acids 549 to 563 in SEQ ID NO:2;

(u) a polynucleotide encoding amino acids 214 to 439 in SEQ ID NO:4;

(v) a polynucleotide encoding amino acids 440 to 529 in SEQ ID NO:4;

(w) a polynucleotide encoding amino acids 530 to 583 in SEQ ID NO:4;

(x) a polynucleotide encoding amino acids 837 to 890 in SEQ ID NO:4;

(y) a polynucleotide encoding amino acids 280 to 606 in SEQ ID NO:4);

(z) a polynucleotide encoding amino acids 529 to 548 in SEQ ID NO:4; and

(aa) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), (x), (y), or (z).

2. An isolated nucleic acid molecule comprising a polynucleotide which encodes the amino acid sequence of an epitope-bearing portion of the METH1 polypeptide of SEQ ID NO:2 or the METH2 polypeptide of SEQ ID NO:4.

3. An isolated nucleic acid molecule, comprising a polynucleotide selected from the group consisting of:

(a) 50 contiguous nucleotides of the coding region of SEQ ID NO:1, provided that said nucleotide sequence is not any one of SEQ ID NOs:14-41, or any subfragment thereof; and

(b) a nucleotide sequence complementary to the nucleotide sequence in (a).

4. An isolated nucleic acid molecule, comprising a polynucleotide selected from the group consisting of:

(a) 50 contiguous nucleotides of the coding region of SEQ ID NO:3, provided that said nucleotide sequence is not SEQ ID NOs:19-22, 24, 42-77, or any subfragment thereof; and

(b) a nucleotide sequence complementary to the nucleotide sequence in (a).

5. A method for making a recombinant vector comprising inserting an isolated nucleic acid molecule of claim 1 into a vector in operable linkage to a promoter.

6. A recombinant vector produced by the method of claim 5.

7. A method of making a recombinant host cell comprising introducing the recombinant vector of claim 6 into a host cell.

8. A recombinant host cell produced by the method of claim 7.

9. A recombinant method for producing a METH1 or METH2 polypeptide, comprising culturing the recombinant host cell of claim 8 under conditions such that said polypeptide is expressed and recovering said polypeptide.

10. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acids 1 to 950 in SEQ ID NO:2;

(b) amino acids 2 to 950 in SEQ ID NO:2;

(c) amino acids 29 to 950 in SEQ ID NO:2;

(d) amino acids 30 to 950 in SEQ ID NO:2;

(d) the amino acid sequence of the METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(e) the amino acid sequence of the mature METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(f) amino acids 1 to 890 in SEQ ID NO:4;

(g) amino acids 2 to 890 in SEQ ID NO:4;

(h) amino acids 24 to 890 in SEQ ID NO:4;

(i) amino acids 112 to 890 in SEQ ID NO:4;

(j) an amino acid sequence of the METH2 polypeptide having the amino acid sequence encoded by the METH2 cDNA clone contained in ATCC Deposit No. 209582;

(k) an amino acid sequence of the mature METH2 polypeptide having the amino acid sequence encoded by the METH2 cDNA clone contained in ATCC Deposit No. 209582;

(l) the amino acid sequence of a polypeptide variant created by altering a polypeptide of (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), or (k), wherein:

(i) said altering includes an amino acid insertion, deletion, or substitution, or any combination thereof; and

(ii) the number of alterations is equal to or less than 5% of the total number of amino acids present in the unaltered amino acid sequence;

(m) amino acids 235 to 459 in SEQ ID NO:2;

(n) amino acids 460 to 544 in SEQ ID NO:2;

(o) amino acids 545 to 598 in SEQ ID NO:2;

(p) amino acids 841 to 894 in SEQ ID NO:2;

(q) amino acids 895 to 934 in SEQ ID NO:2;

(r) amino acids 536 to 613 in SEQ ID NO:2;

(s) amino acids 549 to 563 in SEQ ID NO:2;

(t) amino acids 214 to 439 in SEQ ID NO:4;

(u) amino acids 440 to 529 in SEQ ID NO:4;

(v) amino acids 530 to 583 in SEQ ID NO:4;

(w) amino acids 837 to 890 in SEQ ID NO:4;

(x) amino acids 280 to 606 in SEQ ID NO:4;

(y) amino acids 529 to 548 in SEQ ID NO:4;

(z) the amino acid sequence of an epitope-bearing portion of any one of the polypeptides of (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), (x), or (y).

11. The isolated polypeptide of claim 10, which is produced in a recombinant host cell.

12. The isolated polypeptide of claim 11, wherein said recombinant host cell is mammalian.

13. An isolated nucleic acid molecule comprising a polynucleotide encoding a METH1 or METH2 polypeptide wherein, except for one to fifty conservative amino acid substitutions, said polypeptide has a sequence selected from the group consisting of:

(a) amino acids from about 1 to about 950 in SEQ ID NO:2;

(b) amino acids from about 2 to about 950 in SEQ ID NO:2;

(c) amino acids from about 29 to about 950 in SEQ ID NO:2;

(d) amino acids from about 30 to about 950 in SEQ ID NO:2;

(e) the amino acid sequence of the METH1 polypeptide as encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(f) the amino acid sequence of the mature METH1 polypeptide as encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(g) amino acids from about 1 to about 890 in SEQ ID NO:4;

(h) amino acids from about 2 to about 890 in SEQ ID NO:4;

(i) amino acids from about 24 to 890 in SEQ ID NO:4;

(j) amino acids from about 112 to about 890 in SEQ ID NO:4;

(k) the amino acid sequence of the METH2 polypeptide as encoded by the cDNA clone contained in ATCC Deposit No. 209582; and

(l) the amino acid sequence of the mature METH2 polypeptide as encoded by the cDNA clone contained in ATCC Deposit No. 209582.

14. An isolated polypeptide wherein, except for one to fifty conservative amino acid substitutions, said polypeptide has a sequence selected from the group consisting of:

(a) amino acids from about 1 to about 950 in SEQ ID NO:2;

(b) amino acids from about 2 to about 950 in SEQ ID NO:2;

(c) amino acids from about 29 to about 950 in SEQ ID NO:2;

(d) amino acids from about 30 to about 950 in SEQ ID NO:2;

(e) the amino acid sequence of the METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(f) the amino acid sequence of the mature METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(g) amino acids from about 1 to about 890 in SEQ ID NO:4;

(h) amino acids from about 2 to about 890 in SEQ ID NO:4;

(i) amino acids from about 24 to about 890 in SEQ ID NO:4;

(j) amino acids from about 112 to about 890 in SEQ ID NO:4;

(k) the amino acid sequence of the METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582;

(l) the amino acid sequence of the mature METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582; and

(m) the amino acid sequence of an epitope-bearing portion of any one of the polypeptides of (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), or (l).

15. An isolated nucleic acid molecule comprising a polynucleotide at least 95% identical to a polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding a polypeptide comprising amino acids 1 to 950 in SEQ ID NO:2;

(b) a polynucleotide encoding a polypeptide comprising amino acids 2 to 950 in SEQ ID NO:2;

(c) a polynucleotide encoding a polypeptide comprising amino acids 29 to 950 in SEQ ID NO:2;

(d) a polynucleotide encoding a polypeptide comprising amino acids 30 to 950 in SEQ ID NO:2;

(e) a polynucleotide comprising a nucleotide sequence encoding the METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(f) a polynucleotide comprising a nucleotide sequence encoding the mature METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(g) a polynucleotide encoding a polypeptide comprising amino acids 1 to 890 in SEQ ID NO:4;

(h) a polynucleotide encoding a polypeptide comprising amino acids 2 to 890 in SEQ ID NO:4;

(i) a polynucleotide encoding a polypeptide comprising amino acids 24 to 890 in SEQ ID NO:4;

(j) a polynucleotide encoding a polypeptide comprising amino acids 112 to 890 in SEQ ID NO:4;

(k) a polynucleotide comprising a nucleotide sequence encoding the METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582;

(l) a polynucleotide comprising a nucleotide sequence encoding the mature METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582; and

(m) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), or (l), wherein

said % identity is calculated using the FASTDB computer program, with the parameters: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5,

Gap Size Penalty=0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

16. An isolated polypeptide comprising a polypeptide having 95% identity to a polypeptide having an amino acid sequence selected from the group consisting of:

(a) amino acids from about 1 to about 950 in SEQ ID NO:2;

(b) amino acids from about 2 to about 950 in SEQ ID NO:2;

(c) amino acids from about 29 to about 950 in SEQ ID NO:2;

(d) amino acids from about 30 to about 950 in SEQ ID NO:2;

(e) the amino acid sequence of the METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(f) the amino acid sequence of the mature METH1 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209581;

(g) amino acids from about 1 to about 890 in SEQ ID NO:4;

(h) amino acids from about 2 to about 890 in SEQ ID NO:4;

(i) amino acids from about 24 to about 890 in SEQ ID NO:4;

(j) amino acids from about 112 to about 890 in SEQ ID NO:4;

(k) the amino acid sequence of the METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582; and

(l) the amino acid sequence of the mature METH2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209582;

wherein

said % identity is calculated using the FASTDB computer program, with the parameters: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5,

```
ATGTGGGGGCCTTGGGGAGACTGTTCGAGAACGTGCGGTGGAGGAGTCCAGTACACGATGAGGGAATGTGACAACCCA
 M  W  G  P  W  G  D  C  S  R  T  C  G  G  G  V  Q  Y  T  M  R  E  C  D  N  P

GTCCCAAAGAATGGAGGGAAGTACTGTGAAGGCAAACGAGTGCGCTACAGATCCTGTAACCTTGAGGACTGTCCAGAC
 V  P  K  N  G  G  K  Y  C  E  G  K  R  V  R  Y  R  S  C  N  L  E  D  C  P  D

AATAATGGAAAAACCTTTAGAGAGGAACAATGTGAAGCACACAACGAGTTTTCAAAAGCTTCCTTTGGGAGTGGGCCT
 N  N  G  K  T  F  R  E  E  Q  C  E  A  H  N  E  F  S  K  A  S  F  G  S  G  P

GCGGTGGAATGGATTCCCAAGTACGCTGGCGTCTCACCAAAGGACAGGTGCAAGCTCATCTGCCAAGCCAAAGGCATT
 A  V  E  W  I  P  K  Y  A  G  V  S  P  K  D  R  C  K  L  I  C  Q  A  K  G  I

GGCTACTTCTTCGTTTTGCAGCCCAAGGTTGTAGATGGTACTCCATGTAGCCCAGATTCCACCTCTGTCTGTGTGCAA
 G  Y  F  F  V  L  Q  P  K  V  V  D  G  T  P  C  S  P  D  S  T  S  V  C  V  Q

GGACAGTGTGTAAAAGCTGGTTGTGATCGCATCATAGACTCCAAAAAGAAGTTTGATAAATGTGGTGTTTGCGGGGGA
 G  Q  C  V  K  A  G  C  D  R  I  I  D  S  K  K  K  F  D  K  C  G  V  C  G  G

AATGGATCTACTTGTAAAAAAATATCAGGATCAGTTACTAGTGCAAAACCTGGATATCATGATATCATCACAATTCCA
 N  G  S  T  C  K  K  I  S  G  S  V  T  S  A  K  P  G  Y  H  D  I  I  T  I  P

ACTGGAGCCACCAACATCGAAGTGAAACAGCGGAACCAGAGGGGATCCAGGAACAATGGCAGCTTTCTTGCCATCAAA
 T  G  A  T  N  I  E  V  K  Q  R  N  Q  R  G  S  R  N  N  G  S  F  L  A  I  K

GCTGCTGATGGCACATATATTCTTAATGGTGACTACACTTTGTCCACCTTAGAGCAAGACATTATGTACAAAGGTGTT
 A  A  D  G  T  Y  I  L  N  G  D  Y  T  L  S  T  L  E  Q  D  I  M  Y  K  G  V

GTCTTGAGGTACAGCGGCTCCTCTGCGGCATTGGAAAGAATTCGCAGCTTTAGCCCTCTCAAAGAGCCCTTGACCATC
 V  L  R  Y  S  G  S  S  A  A  L  E  R  I  R  S  F  S  P  L  K  E  P  L  T  I

CAGGTTCTTACTGTGGGCAATGCCCTTCGACCTAAAATTAAATACACCTACTTCGTAAAGAAGAAGAAGGAATCTTTC
 Q  V  L  T  V  G  N  A  L  R  P  K  I  K  Y  T  Y  F  V  K  K  K  K  E  S  F

AATGCTATCCCCACTTTTTCAGCATGGGTCATTGAAGAGTGGGGCGAATGTTCTAAGTCATGTGAATTGGGTTGGCAG
 N  A  I  P  T  F  S  A  W  V  I  E  E  W  G  E  C  S  K  S  C  E  L  G  W  Q

AGAAGACTGGTAGAATGCCGAGACATTAATGGACAGCCTGCTTCCGAGTGTGCAAAGGAAGTGAAGCCAGCCAGCACC
 R  R  L  V  E  C  R  D  I  N  G  Q  P  A  S  E  C  A  K  E  V  K  P  A  S  T

AGACCTTGTGCAGACCATCCCTGCCCCCAGTGGCAGCTGGGGGAGTGGTCATCATGTTCTAAGACCTGTGGGAAGGGT
 R  P  C  A  D  H  P  C  P  Q  W  Q  L  G  E  W  S  S  C  S  K  T  C  G  K  G

TACAAAAAAAAGAAGCTTGAAGTGTCTGTCCCATGATGGAGGGGTGTTATCTCATGAGAGCTGTGATCCTTTAAAGAAA
 Y  K  K  R  S  L  K  C  L  S  H  D  G  G  V  L  S  H  E  S  C  D  P  L  K  K

CCTAAACATTTCATAGACTTTTGCACAATGGCAGAATGCAGTTAAGTGGTTTAAGTGGTGTTAGCTTTGAGGCAAGGC
 P  K  H  F  I  D  F  C  T  M  A  E  C  S

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```

FIGURE 1

```
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 M  F  P  A  P  A  A  P  R  W  L  P  F  L  L  L  L  L  L  L  L  L  P  L  A  R

GGCGCCCCGGCCCGGCCCGCAGCCGGGGGGCAGGCCTCGGAGCTGGTGGTGCCCACGCGGTTGCCCGGCAGCGCGGGC
 G  A  P  A  R  P  A  A  G  G  Q  A  S  E  L  V  V  P  T  R  L  P  G  S  A  G

GAGCTCGCGCTCCACCTGTCCGCCTTCGGCAAGGGCTTCGTGTTGCGCCTGGCGCCCGACGACAGCTTCCTGGCGCCC
 E  L  A  L  H  L  S  A  F  G  K  G  F  V  L  R  L  A  P  D  D  S  F  L  A  P

GAGTTCAAGATCGAGCGCCTCGGGGGCTCCGGCCGGGCGACCGGGGGCGAGCGGGGGCTGCGCGGCTGTTTTTTTTCC
 E  F  K  I  E  R  L  G  G  S  G  R  A  T  G  G  E  R  G  L  R  G  C  F  F  S

GGCACCGTGAATGGGGAGCCCGAGTCGCTGGCGGCGGTCAGCCTGTGCCGCGGGCTGAGCGGCTCCTTCCTGCTGGAC
 G  T  V  N  G  E  P  E  S  L  A  A  V  S  L  C  R  G  L  S  G  S  F  L  L  D

GGCGAGGAGTTCACCATCCAGCCGCAGGGCGCGGGGGGCTCCCTGGCTCAGCCGCACCGCCTGCAGCGCTGGGGTCCC
 G  E  E  F  T  I  Q  P  Q  G  A  G  G  S  L  A  Q  P  H  R  L  Q  R  W  G  P

GCCGGAGCCCGCCCCCTCCCGCGAGGACCCGAGTGGGAGGTGGAGACGGGAGAGGGTCAGAGGCAGGAGAGAGGAGAC
 A  G  A  R  P  L  P  R  G  P  E  W  E  V  E  T  G  E  G  Q  R  Q  E  R  G  D

CACCAGGAGGACAGCGAGGAGGAGAGCCAAGAAGAGGAGGCAGAAGGCGCTAGCGAGCCGCCACCGCCCCTGGGGGCC
 H  Q  E  D  S  E  E  E  S  Q  E  E  E  A  E  G  A  S  E  P  P  P  P  L  G  A

ACGAGTAGGACCAAGCGGTTTGTGTCTGAGGCGCGCTTCGTGGAGACGCTGCTGGTGGCCGATGCGTCCATGGCTGCC
 T  S  R  T  K  R  F  V  S  E  A  R  F  V  E  T  L  L  V  A  D  A  S  M  A  A

TTCTACGGGGCCGACCTGCAGAACCACATCCTGACGTTAATGTCTGTGGCAGCCCGAATCTACAAGCACCCCAGCATC
 F  Y  G  A  D  L  Q  N  H  I  L  T  L  M  S  V  A  A  R  I  Y  K  H  P  S  I

AAGAATTCCATCAACCTGATGGTGGTAAAAGTGCTGATCGTAGAAGATGAAAAATGGGGCCCAGAGGTGTCCGACAAT
 K  N  S  I  N  L  M  V  V  K  V  L  I  V  E  D  E  K  W  G  P  E  V  S  D  N

GGGGGGCTTACACTGCGTAACTTCTGCAACTGGCAGCGGCGTTTCAACCAGCCCAGCGACCGCCACCCAGAGCACTAC
 G  G  L  T  L  R  N  F  C  N  W  Q  R  R  F  N  Q  P  S  D  R  H  P  E  H  Y

GACACGGCCATCCTGCTCACCAGACAGAACTTCTGTGGGCAGGAGGGGCTGTGTGACACCCTGGGTGTGGCAGACATC
 D  T  A  I  L  L  T  R  Q  N  F  C  G  Q  E  G  L  C  D  T  L  G  V  A  D  I

GGGACCATTTGTGACCCCAACAAAAGCTGCTCCGTGATCGAGGATGAGGGGCTCCAGGCGGCCCACACCCTGGCCCAT
 G  T  I  C  D  P  N  K  S  C  S  V  I  E  D  E  G  L  Q  A  A  H  T  L  A  H

GAACTAGGGCACGTCCTCAGCATGCCCCACGACGACTCCAAGCCCTGCACACGGCTCTTCGGGCCCATGGGCAAGCAC
 E  L  G  H  V  L  S  M  P  H  D  D  S  K  P  C  T  R  L  F  G  P  M  G  K  H

CACGTGATGGCACCGCTGTTCGTCCACCTGAACCAGACGCTGCCCTGGTCCCCCTGCAGCGCCATGTATCTCACAGAG
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CGCATGGCCCTGTACCAGCTGGACCAGCAGTGCAGGCAGATCTTTGGGCCGGATTTCCGCCACTGCCCCAACACCTCT
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GCTCAGGACGTCTGCGCCCAGCTTTGGTGCCACACTGATGGGGCTGAGCCCCTGTGCCACACGAAGAATGGCAGCCTG
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 P  W  A  D  G  T  P  C  G  P  G  H  L  C  S  E  G  S  C  L  P  E  E  E  V  E

AGGCCCAAGCCCGTGGTAGATGGAGGCTGGGCACCGTGGGGACCCTGGGGAGAATGTTCTCGGACCTGTGGAGGAGGA
 R  P  K  P  V  V  D  G  G  W  A  P  W  G  P  W  G  E  C  S  R  T  C  G  G  G
```

FIGURE 2

```
GTACAGTTTTCACACCGTGAGTGCAAGGACCCCGAGCCTCAGAATGGAGGAAGATACTGCCTGGGTCGGAGAGCCAAG
 V  Q  F  S  H  R  E  C  K  D  P  E  P  Q  N  G  G  R  Y  C  L  G  R  R  A  K

TACCAGTCATGCCACACGGAGGAATGCCCCCCTGACGGGAAAAGCTTCAGGGAGCAGCAGTGTGAGAAGTATAATGCC
 Y  Q  S  C  H  T  E  E  C  P  P  D  G  K  S  F  R  E  Q  Q  C  E  K  Y  N  A

TACAATTACACTGACATGGACGGGAATCTCCTGCAGTGGGTCCCCAAGTATGCTGGGGTGTCCCCCCGGGACCGCTGC
 Y  N  Y  T  D  M  D  G  N  L  L  Q  W  V  P  K  Y  A  G  V  S  P  R  D  R  C

AAGTTGTTCTGCCGAGCCCGGGGGAGGAGCGAGTTCAAAGTGTTCGAGGCCAAGGTGATTGATGGCACCCTGTGTGGG
 K  L  F  C  R  A  R  G  R  S  E  F  K  V  F  E  A  K  V  I  D  G  T  L  C  G

CCAGAAACACTGGCCATCTGTGTCCGTGGCCAGTGTGTCAAGGCCGGCTGTGACCATGTGGTGGACTCGCCTCGGAAG
 P  E  T  L  A  I  C  V  R  G  Q  C  V  K  A  G  C  D  H  V  V  D  S  P  R  K

CTGGACAAATGCGGGGGTGTGTGGGGGCAAAGGCAACTCCTGCAGGAAGGTCTCCGGGTCCCTCACCCCCACCAATTAT
 L  D  K  C  G  V  C  G  G  K  G  N  S  C  R  K  V  S  G  S  L  T  P  T  N  Y

GGCTACAATGACATTGTCACCATCCCAGCTGGTGCCACTAATATTGACGTGAAGCAGCGGAGCCACCCGGGTGTGCAG
 G  Y  N  D  I  V  T  I  P  A  G  A  T  N  I  D  V  K  Q  R  S  H  P  G  V  Q

AACGATGGGAACTACCTGGCGCTGAAGACGGCTGATGGGCAGTACCTGCTCAACGGCAACCTGGCCATCTCTGCCATA
 N  D  G  N  Y  L  A  L  K  T  A  D  G  Q  Y  L  L  N  G  N  L  A  I  S  A  I

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 R  P  L  P  E  P  L  T  V  Q  L  L  T  V  P  G  E  V  F  P  P  K  V  K  Y  T

TTCTTTGTTCCTAATGACGTGGACTTTAGCATGCAGAGCAGCAAAGAGAGAGCAACCACCAACATCATCCAGCCGCTG
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 L  H  A  Q  W  V  L  G  D  W  S  E  C  S  S  T  C  G  A  G  W  Q  R  R  T  V

GAGTGCAGGGACCCCTCCGGCCAGGCCTCTGCCACCTGCAACAAGGCTCTGAAACCCGAGGATGCCAAGCCCTGCGAA
 E  C  R  D  P  S  G  Q  A  S  A  T  C  N  K  A  L  K  P  E  D  A  K  P  C  E

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 S  Q  L  C  P  L

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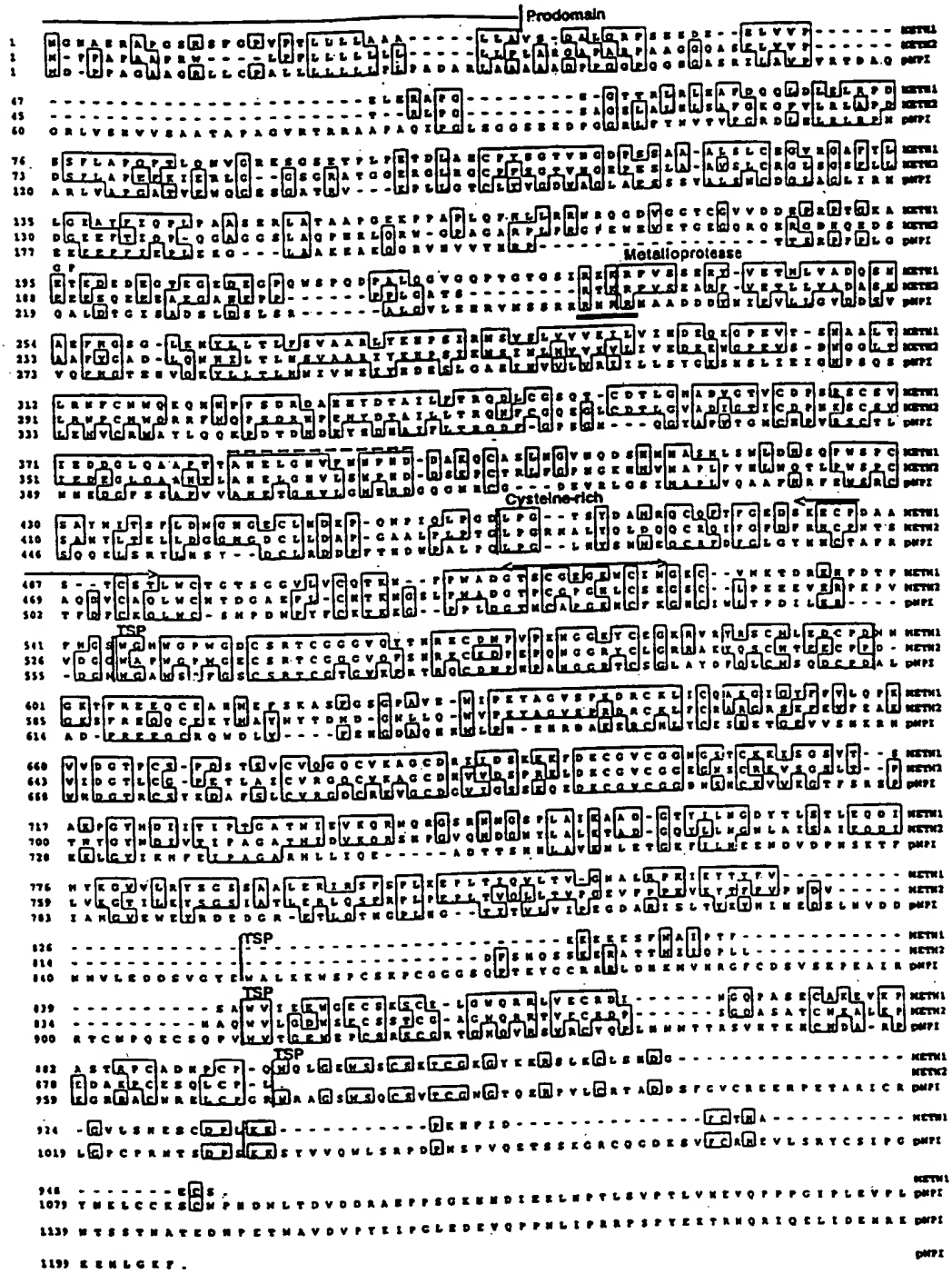
FIGURE 2

WO 99/37660



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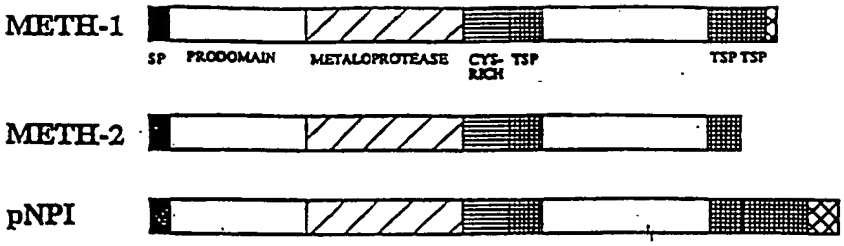

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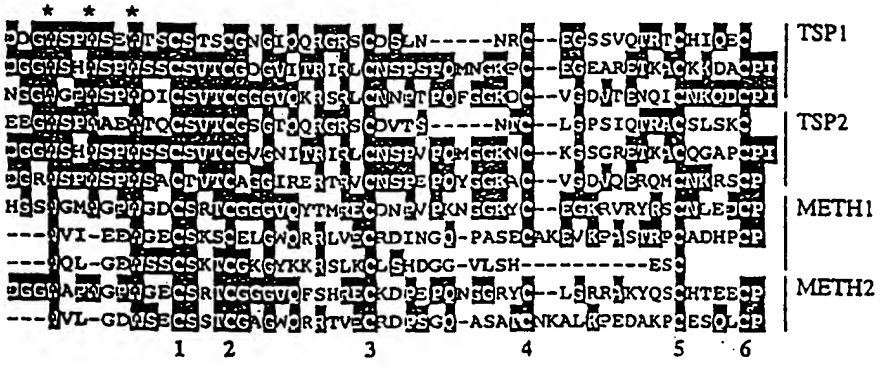

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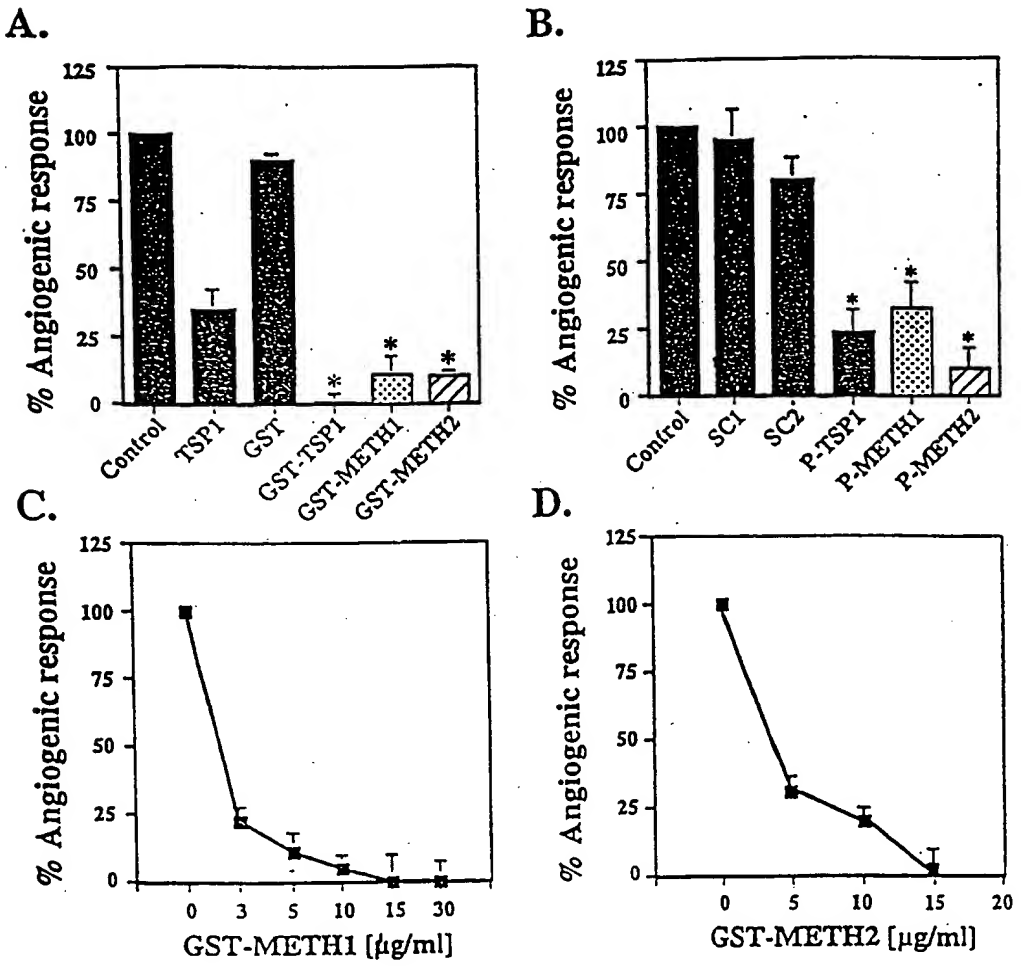

A.
% Angiogenic response
125
100
75
50
25
0
Control
TSP1
GST
GST-TSP1
GST-METH1
GST-METH2
B.
% Angiogenic response
Control
SC1
SC2
P-TSP1
P-METH1
P-METH2
C.
% Angiogenic response
0 3 5 10 15 30
GST-METH1 [µg/ml]
D.
% Angiogenic response
0 5 10 15 20
GST-METH2 [µg/ml]

Figure 6

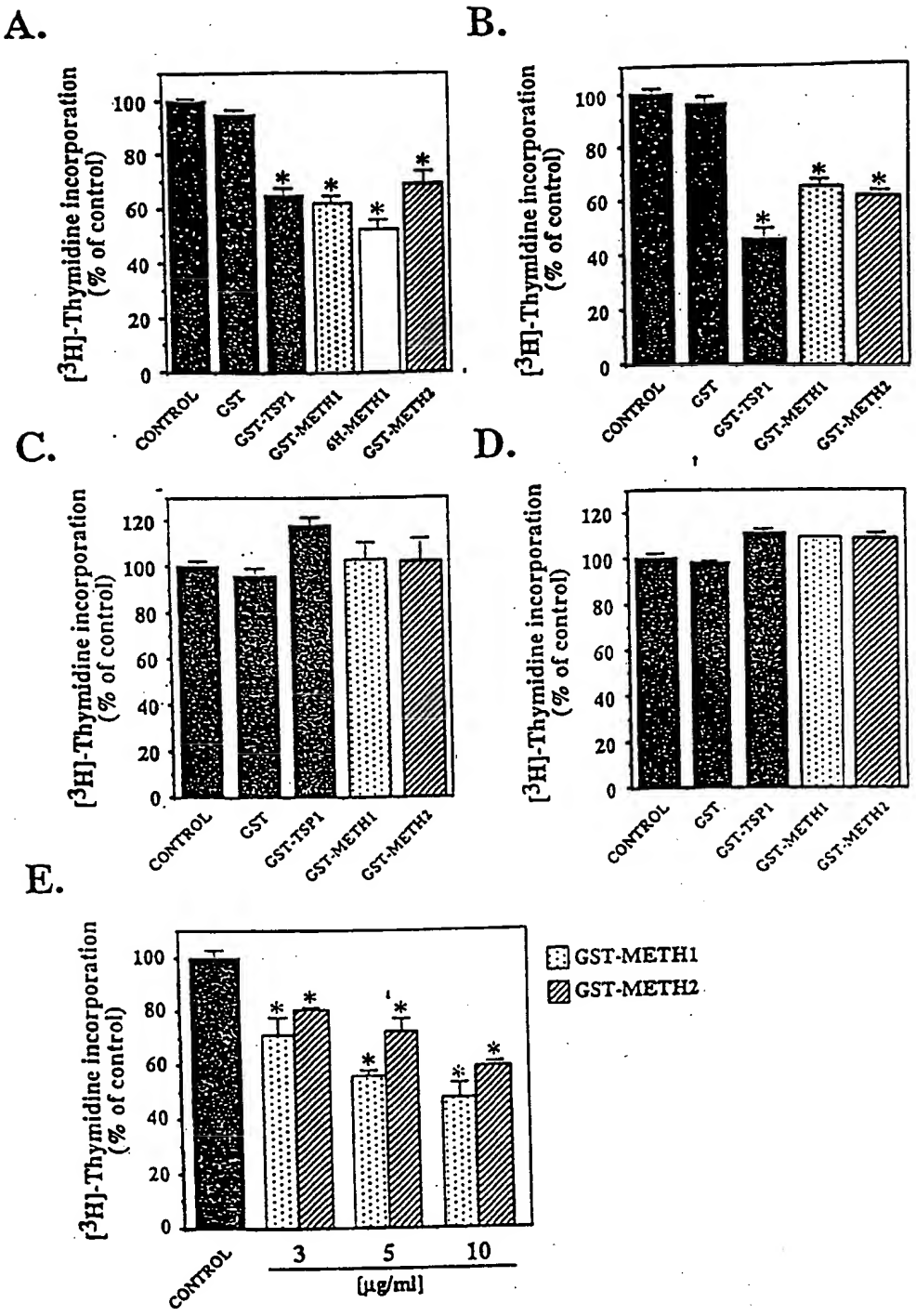

A.
B.
C.
D.
E.
[3H]-Thymidine incorporation (% of control)
CONTROL
GST
GST-TSP1
GST-METH1
6H-METH1
GST-METH2
GST-METH1
GST-METH2
[µg/ml]
3
5
10

Figure 7

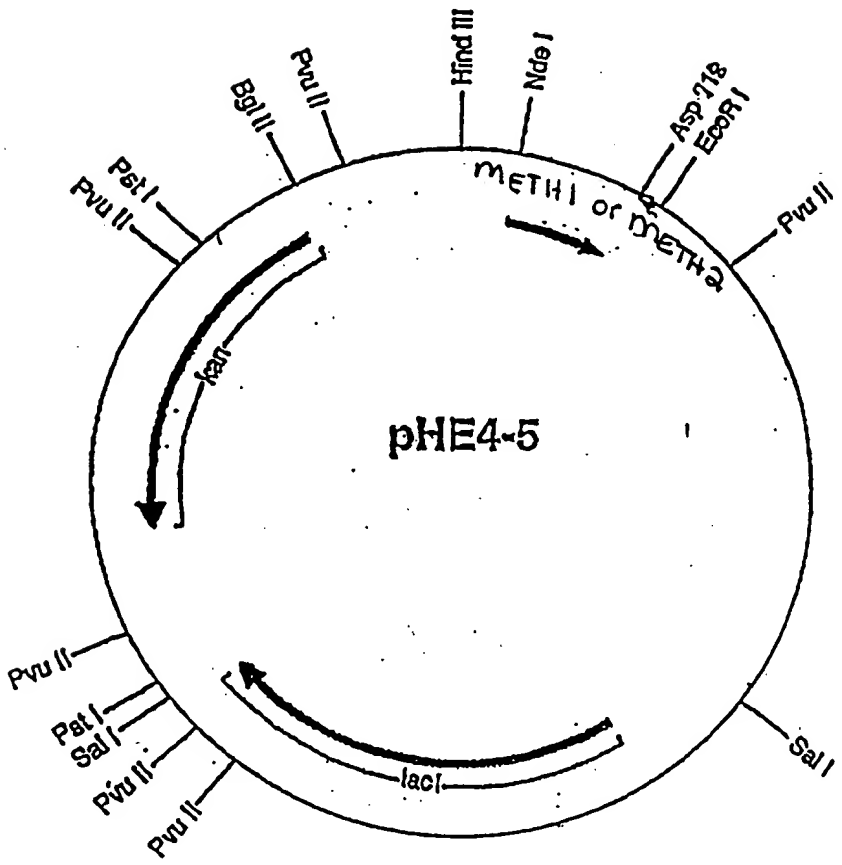
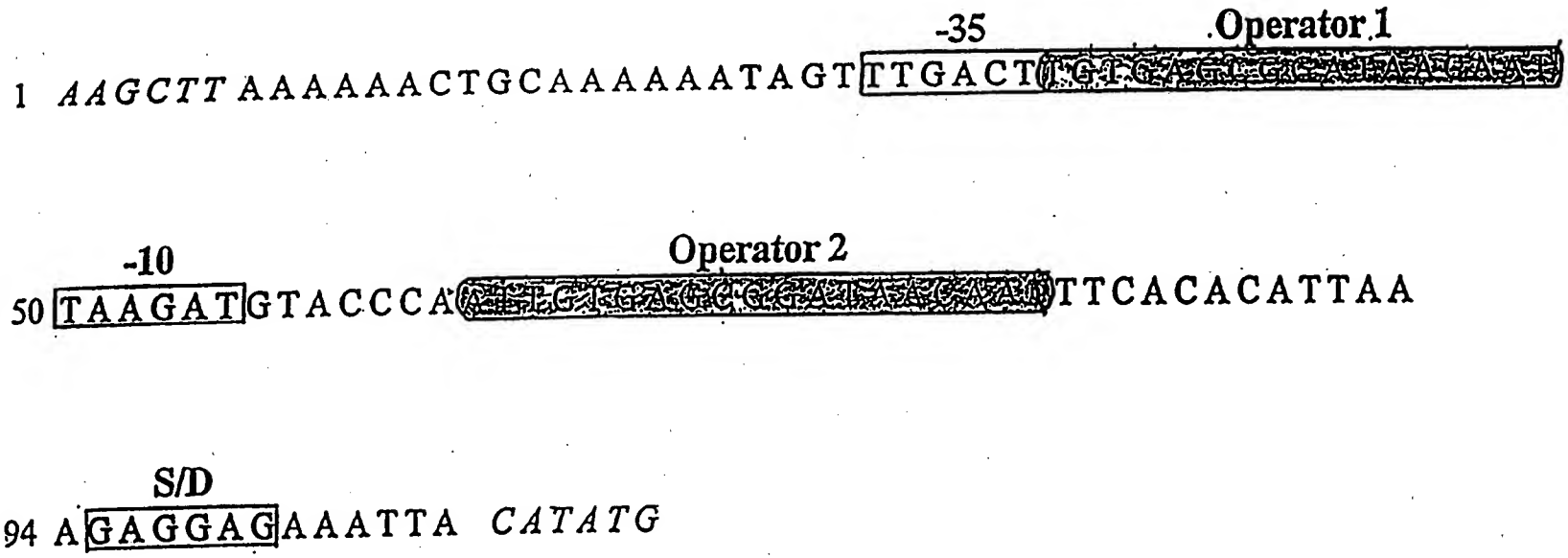

Hind III
Nde I
Asp 718
EcoR I
Pvu II
Bgl II
Pvu II
Pst I
Pvu II
METH1 or METH2
pHE4-5
kan
lacI
Pvu II
Pst I
Sal I
Pvu II
Pvu II
Sal I

FIGURE 8

Figure 9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Operator 1
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-10
Operator 2
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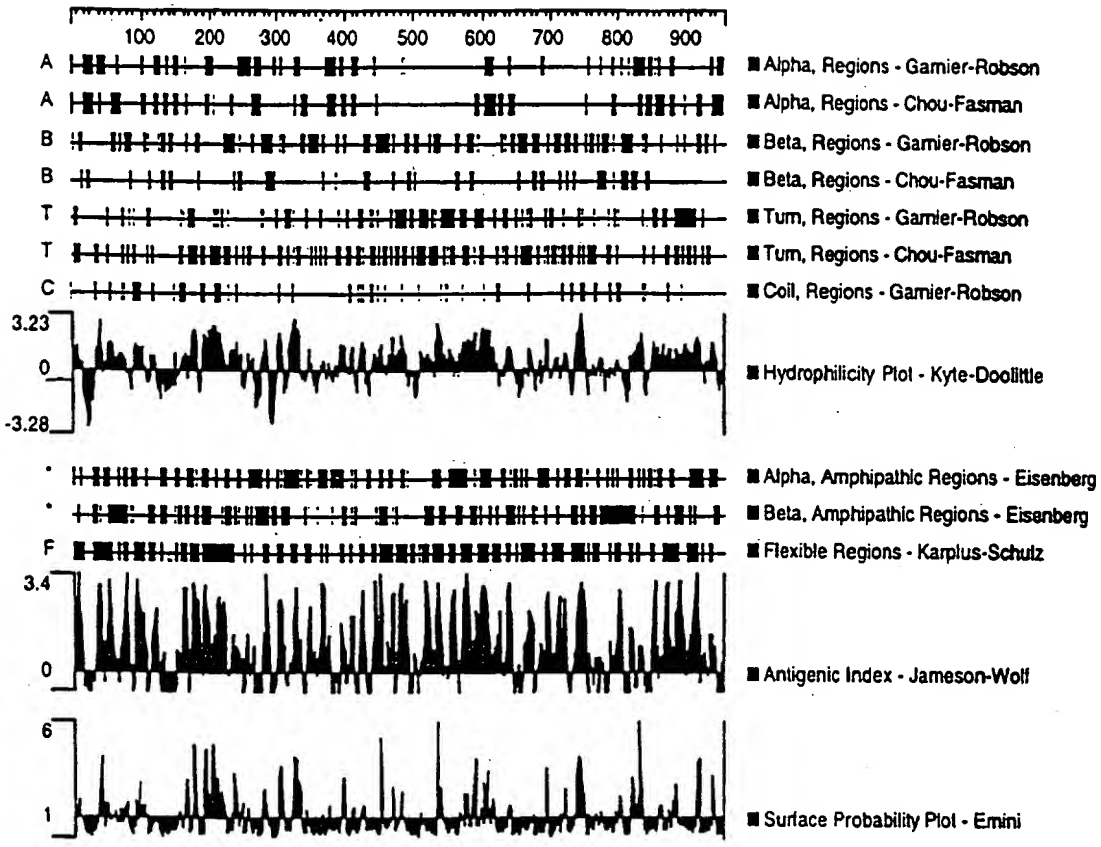
S/D
94 A GAGGAG AAATTA CATATG

Figure 10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200
300
400
500
600
700
800
900
A
A
B
B
T
T
C
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
3.23
0
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Hydrophilicity Plot - Kyte-Doolittle
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
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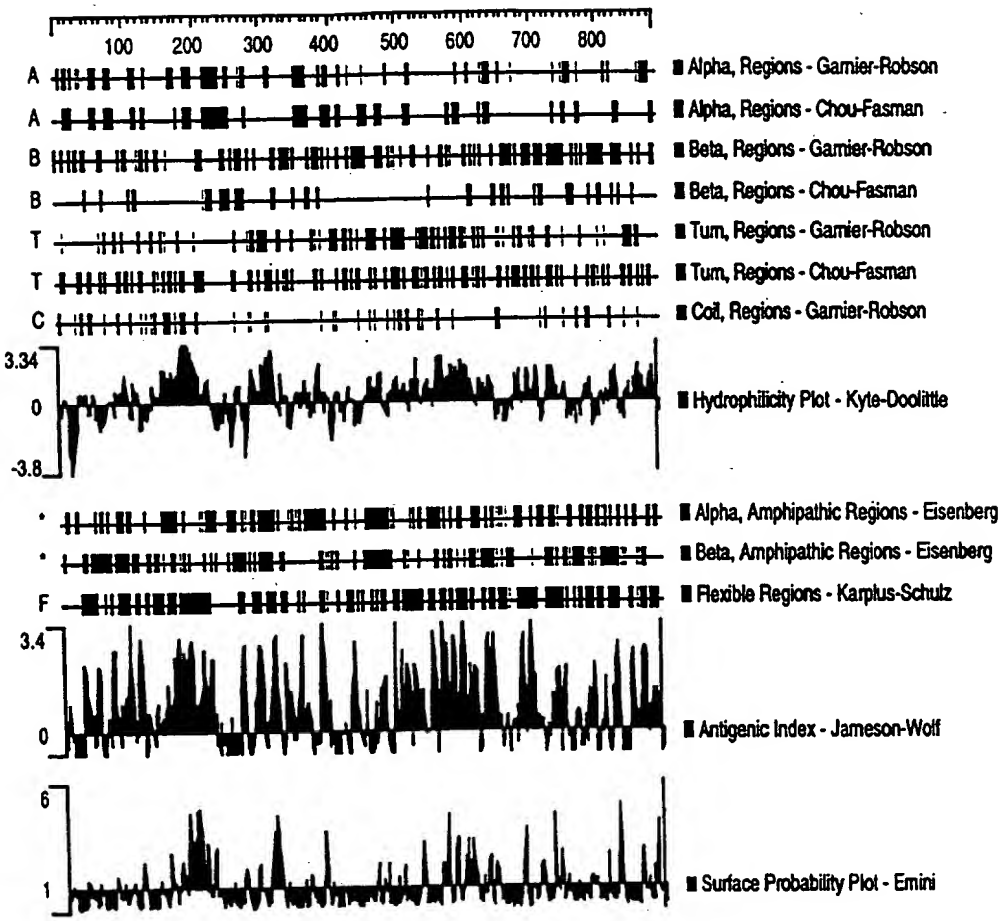
Flexible Regions - Karplus-Schulz
3.4
0
Antigenic Index - Jameson-Wolf
6
1
Surface Probability Plot - Emini

Figure 11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200
300
400
500
600
700
800
A
Alpha, Regions - Garnier-Robson
A
Alpha, Regions - Chou-Fasman
B
Beta, Regions - Garnier-Robson
B
Beta, Regions - Chou-Fasman
T
Turn, Regions - Garnier-Robson
T
Turn, Regions - Chou-Fasman
C
Coil, Regions - Garnier-Robson
3.34
0
-3.8
Hydrophilicity Plot - Kyte-Doolittle
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
F
Flexible Regions - Karplus-Schulz
3.4
0
Antigenic Index - Jameson-Wolf
6
1
Surface Probability Plot - Emini

SEQUENCE LISTING

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Ruben, Steven M.

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ccc acg ctg ctg ctg ctc gcc gcg gcg cta ctg gcc gtg tcg gac gca   96
Pro Thr Leu Leu Leu Leu Ala Ala Ala Leu Leu Ala Val Ser Asp Ala
            20                  25                  30

ctc ggg cgc ccc tcc gag gag gac gag gag cta gtg gtg ccg gag ctg   144
Leu Gly Arg Pro Ser Glu Glu Asp Glu Glu Leu Val Val Pro Glu Leu
        35                  40                  45

gag cgc gcc ccg gga cac ggg acc acg cgc ctc cgc ctg cac gcc ttt   192
Glu Arg Ala Pro Gly His Gly Thr Thr Arg Leu Arg Leu His Ala Phe
    50                  55                  60

gac cag cag ctg gat ctg gag ctg cgg ccc gac agc agc ttt ttg gcg   240
Asp Gln Gln Leu Asp Leu Glu Leu Arg Pro Asp Ser Ser Phe Leu Ala
65                  70                  75                  80

ccc ggc ttc acg ctc cag aac gtg ggg cgc aaa tcc ggg tcc gag acg   288
Pro Gly Phe Thr Leu Gln Asn Val Gly Arg Lys Ser Gly Ser Glu Thr
                85                  90                  95

ccg ctt ccg gaa acc gac ctg gcg cac tgc ttc tac tcc ggc acc gtg   336
Pro Leu Pro Glu Thr Asp Leu Ala His Cys Phe Tyr Ser Gly Thr Val
            100                 105                 110

aat ggc gat ccc agc tcg gct gcc gcc ctc agc ctc tgc gag ggc gtg   384
Asn Gly Asp Pro Ser Ser Ala Ala Ala Leu Ser Leu Cys Glu Gly Val
        115                 120                 125

cgc ggc gcc ttc tac ctg ctg ggg gag gcg tat ttc atc cag ccg ctg   432
Arg Gly Ala Phe Tyr Leu Leu Gly Glu Ala Tyr Phe Ile Gln Pro Leu
    130                 135                 140

ccc gcc gcc agc gag cgc ctc gcc acc gcc gcc cca ggg gag aag ccg   480
Pro Ala Ala Ser Glu Arg Leu Ala Thr Ala Ala Pro Gly Glu Lys Pro
145                 150                 155                 160

ccg gca cca cta cag ttc cac ctc ctg cgg cgg aat cgg cag ggc gac   528
Pro Ala Pro Leu Gln Phe His Leu Leu Arg Arg Asn Arg Gln Gly Asp
                165                 170                 175

gta ggc ggc acg tgc ggg gtc gtg gac gac gag ccc cgg ccg act ggg   576
Val Gly Gly Thr Cys Gly Val Val Asp Asp Glu Pro Arg Pro Thr Gly
            180                 185                 190

aaa gcg gag acc gaa gac gag gac gaa ggg act gag ggc gag gac gaa   624
Lys Ala Glu Thr Glu Asp Glu Asp Glu Gly Thr Glu Gly Glu Asp Glu
        195                 200                 205

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Pro Thr Gly Thr Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser His
225                 230                 235                 240

cgc tat gtg gaa acc atg ctt gtg gca gac cag tcg atg gca gaa ttc   768
Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Glu Phe
                245                 250                 255

cac ggc agt ggt cta aag cat tac ctt ctc acg ttg ttt tcg gtg gca   816
His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val Ala
            260                 265                 270

gcc aga ttg tac aaa cac ccc agc att cgt aat tca gtt agc ctg gtg   864
Ala Arg Leu Tyr Lys His Pro Ser Ile Arg Asn Ser Val Ser Leu Val
        275                 280                 285

gtg gtg aag atc ttg gtc atc cac gat gaa cag aag ggg ccg gaa gtg   912
Val Val Lys Ile Leu Val Ile His Asp Glu Gln Lys Gly Pro Glu Val
    290                 295                 300

acc tcc aat gct gcc ctc act ctg cgg aac ttt tgc aac tgg cag aag   960
Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln Lys
305                 310                 315                 320

cag cac aac cca ccc agt gac cgg gat gca gag cac tat gac aca gca   1008
Gln His Asn Pro Pro Ser Asp Arg Asp Ala Glu His Tyr Asp Thr Ala
                325                 330                 335

att ctt ttc acc aga cag gac ttg tgt ggg tcc cag aca tgt gat act   1056
Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser Gln Thr Cys Asp Thr
            340                 345                 350

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        355                 360                 365

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Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala His
    370                 375                 380

gaa tta ggc cac gtg ttt aac atg cca cat gat gat gca aag cag tgt   1200
Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys Gln Cys
385                 390                 395                 400

gcc agc ctt aat ggt gtg aac cag gat tcc cac atg atg gcg tca atg   1248
Ala Ser Leu Asn Gly Val Asn Gln Asp Ser His Met Met Ala Ser Met
                405                 410                 415

ctt tcc aac ctg gac cac agc cag cct tgg tct cct tgc agt gcc tac   1296
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```
Leu Ser Asn Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala Tyr
            420                 425                 430

atg att aca tca ttt ctg gat aat ggt cat ggg gaa tgt ttg atg gac   1344
Met Ile Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met Asp
        435                 440                 445

aag cct cag aat ccc ata cag ctc cca ggc gat ctc cct ggc acc tcg   1392
Lys Pro Gln Asn Pro Ile Gln Leu Pro Gly Asp Leu Pro Gly Thr Ser
    450                 455                 460

tac gat gcc aac cgg cag tgc cag ttt aca ttt ggg gag gac tcc aaa   1440
Tyr Asp Ala Asn Arg Gln Cys Gln Phe Thr Phe Gly Glu Asp Ser Lys
465                 470                 475                 480

cac tgc cct gat gca gcc agc aca tgt agc acc ttg tgg tgt acc ggc   1488
His Cys Pro Asp Ala Ala Ser Thr Cys Ser Thr Leu Trp Cys Thr Gly
                485                 490                 495

acc tct ggt ggg gtg ctg gtg tgt caa acc aaa cac ttc ccg tgg gcg   1536
Thr Ser Gly Gly Val Leu Val Cys Gln Thr Lys His Phe Pro Trp Ala
            500                 505                 510

gat ggc acc agc tgt gga gaa ggg aaa tgg tgt atc aac ggc aag tgt   1584
Asp Gly Thr Ser Cys Gly Glu Gly Lys Trp Cys Ile Asn Gly Lys Cys
        515                 520                 525

gtg aac aaa acc gac aga aag cat ttt gat acg cct ttt cat gga agc   1632
Val Asn Lys Thr Asp Arg Lys His Phe Asp Thr Pro Phe His Gly Ser
    530                 535                 540

tgg gga atg tgg ggg cct tgg gga gac tgt tcg aga acg tgc ggt gga   1680
Trp Gly Met Trp Gly Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly
545                 550                 555                 560

gga gtc cag tac acg atg agg gaa tgt gac aac cca gtc cca aag aat   1728
Gly Val Gln Tyr Thr Met Arg Glu Cys Asp Asn Pro Val Pro Lys Asn
                565                 570                 575

gga ggg aag tac tgt gaa ggc aaa cga gtg cgc tac aga tcc tgt aac   1776
Gly Gly Lys Tyr Cys Glu Gly Lys Arg Val Arg Tyr Arg Ser Cys Asn
            580                 585                 590

ctt gag gac tgt cca gac aat aat gga aaa acc ttt aga gag gaa caa   1824
Leu Glu Asp Cys Pro Asp Asn Asn Gly Lys Thr Phe Arg Glu Glu Gln
        595                 600                 605

tgt gaa gca cac aac gag ttt tca aaa gct tcc ttt ggg agt ggg cct   1872
Cys Glu Ala His Asn Glu Phe Ser Lys Ala Ser Phe Gly Ser Gly Pro
    610                 615                 620

gcg gtg gaa tgg att ccc aag tac gct ggc gtc tca cca aag gac agg   1920
```

```
Ala Val Glu Trp Ile Pro Lys Tyr Ala Gly Val Ser Pro Lys Asp Arg
625                 630                 635                 640

tgc aag ctc atc tgc caa gcc aaa ggc att ggc tac ttc ttc gtt ttg   1968
Cys Lys Leu Ile Cys Gln Ala Lys Gly Ile Gly Tyr Phe Phe Val Leu
                645                 650                 655

cag ccc aag gtt gta gat ggt act cca tgt agc cca gat tcc acc tct   2016
Gln Pro Lys Val Val Asp Gly Thr Pro Cys Ser Pro Asp Ser Thr Ser
            660                 665                 670

gtc tgt gtg caa gga cag tgt gta aaa gct ggt tgt gat cgc atc ata   2064
Val Cys Val Gln Gly Gln Cys Val Lys Ala Gly Cys Asp Arg Ile Ile
        675                 680                 685

gac tcc aaa aag aag ttt gat aaa tgt ggt gtt tgc ggg gga aat gga   2112
Asp Ser Lys Lys Lys Phe Asp Lys Cys Gly Val Cys Gly Gly Asn Gly
    690                 695                 700

tct act tgt aaa aaa ata tca gga tca gtt act agt gca aaa cct gga   2160
Ser Thr Cys Lys Lys Ile Ser Gly Ser Val Thr Ser Ala Lys Pro Gly
705                 710                 715                 720

tat cat gat atc atc aca att cca act gga gcc acc aac atc gaa gtg   2208
Tyr His Asp Ile Ile Thr Ile Pro Thr Gly Ala Thr Asn Ile Glu Val
                725                 730                 735

aaa cag cgg aac cag agg gga tcc agg aac aat ggc agc ttt ctt gcc   2256
Lys Gln Arg Asn Gln Arg Gly Ser Arg Asn Asn Gly Ser Phe Leu Ala
            740                 745                 750

atc aaa gct gct gat ggc aca tat att ctt aat ggt gac tac act ttg   2304
Ile Lys Ala Ala Asp Gly Thr Tyr Ile Leu Asn Gly Asp Tyr Thr Leu
        755                 760                 765

tcc acc tta gag caa gac att atg tac aaa ggt gtt gtc ttg agg tac   2352
Ser Thr Leu Glu Gln Asp Ile Met Tyr Lys Gly Val Val Leu Arg Tyr
    770                 775                 780

agc ggc tcc tct gcg gca ttg gaa aga att cgc agc ttt agc cct ctc   2400
Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg Ser Phe Ser Pro Leu
785                 790                 795                 800

aaa gag ccc ttg acc atc cag gtt ctt act gtg ggc aat gcc ctt cga   2448
Lys Glu Pro Leu Thr Ile Gln Val Leu Thr Val Gly Asn Ala Leu Arg
                805                 810                 815

cct aaa att aaa tac acc tac ttc gta aag aag aag aag gaa tct ttc   2496
Pro Lys Ile Lys Tyr Thr Tyr Phe Val Lys Lys Lys Lys Glu Ser Phe
            820                 825                 830

aat gct atc ccc act ttt tca gca tgg gtc att gaa gag tgg ggc gaa   2544
```

```
Asn Ala Ile Pro Thr Phe Ser Ala Trp Val Ile Glu Glu Trp Gly Glu
        835                 840                 845

tgt tct aag tca tgt gaa ttg ggt tgg cag aga aga ctg gta gaa tgc   2592
Cys Ser Lys Ser Cys Glu Leu Gly Trp Gln Arg Arg Leu Val Glu Cys
    850                 855                 860

cga gac att aat gga cag cct gct tcc gag tgt gca aag gaa gtg aag   2640
Arg Asp Ile Asn Gly Gln Pro Ala Ser Glu Cys Ala Lys Glu Val Lys
865                 870                 875                 880

cca gcc agc acc aga cct tgt gca gac cat ccc tgc ccc cag tgg cag   2688
Pro Ala Ser Thr Arg Pro Cys Ala Asp His Pro Cys Pro Gln Trp Gln
                885                 890                 895

ctg ggg gag tgg tca tca tgt tct aag acc tgt ggg aag ggt tac aaa   2736
Leu Gly Glu Trp Ser Ser Cys Ser Lys Thr Cys Gly Lys Gly Tyr Lys
            900                 905                 910

aaa aga agc ttg aag tgt ctg tcc cat gat gga ggg gtg tta tct cat   2784
Lys Arg Ser Leu Lys Cys Leu Ser His Asp Gly Gly Val Leu Ser His
        915                 920                 925

gag agc tgt gat cct tta aag aaa cct aaa cat ttc ata gac ttt tgc   2832
Glu Ser Cys Asp Pro Leu Lys Lys Pro Lys His Phe Ile Asp Phe Cys
    930                 935                 940

aca atg gca gaa tgc agt taa gtggtttaag tggtgttagc tttgaggcaa      2883
Thr Met Ala Glu Cys Ser
945                 950

ggcaaagtga ggaagggctg gtgcagggaa agcaagaagg ctggagggat ccagcgtatc 2943

ttgccagtaa ccagtgaggt gtatcagtaa ggtgggatta tgggggtaga tagaaaagga 3003

gttgaatcat cagagtaaac tgccagttgc aaatttgata ggatagttag tgaggattat 3063

taacctctga gcagtgatat agcataataa ancccgggc attattatta ttatttcttt 3123

tgttacatct attacaagtt tagaaaaaac aaagcaattg tcaaaaaaaa aaaaaaaaaa 3183

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catgntgtca tnagtctn                                               3261


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Pro Thr Leu Leu Leu Leu Ala Ala Ala Leu Leu Ala Val Ser Asp Ala
            20                  25                  30

Leu Gly Arg Pro Ser Glu Glu Asp Glu Glu Leu Val Val Pro Glu Leu
        35                  40                  45

Glu Arg Ala Pro Gly His Gly Thr Thr Arg Leu Arg Leu His Ala Phe
    50                  55                  60

Asp Gln Gln Leu Asp Leu Glu Leu Arg Pro Asp Ser Ser Phe Leu Ala
65                  70                  75                  80

Pro Gly Phe Thr Leu Gln Asn Val Gly Arg Lys Ser Gly Ser Glu Thr
                85                  90                  95

Pro Leu Pro Glu Thr Asp Leu Ala His Cys Phe Tyr Ser Gly Thr Val
            100                 105                 110

Asn Gly Asp Pro Ser Ser Ala Ala Ala Leu Ser Leu Cys Glu Gly Val
        115                 120                 125

Arg Gly Ala Phe Tyr Leu Leu Gly Glu Ala Tyr Phe Ile Gln Pro Leu
    130                 135                 140

Pro Ala Ala Ser Glu Arg Leu Ala Thr Ala Ala Pro Gly Glu Lys Pro
145                 150                 155                 160

Pro Ala Pro Leu Gln Phe His Leu Leu Arg Arg Asn Arg Gln Gly Asp
                165                 170                 175

Val Gly Gly Thr Cys Gly Val Val Asp Asp Glu Pro Arg Pro Thr Gly
            180                 185                 190

Lys Ala Glu Thr Glu Asp Glu Asp Glu Gly Thr Glu Gly Glu Asp Glu
        195                 200                 205

Gly Pro Gln Trp Ser Pro Gln Asp Pro Ala Leu Gln Gly Val Gly Gln
    210                 215                 220

Pro Thr Gly Thr Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser His
225                 230                 235                 240

Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Glu Phe
                245                 250                 255

His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val Ala
            260                 265                 270

Ala Arg Leu Tyr Lys His Pro Ser Ile Arg Asn Ser Val Ser Leu Val
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      275                 280                 285

Val Val Lys Ile Leu Val Ile His Asp Glu Gln Lys Gly Pro Glu Val
    290                 295                 300

Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln Lys
305                 310                 315                 320

Gln His Asn Pro Pro Ser Asp Arg Asp Ala Glu His Tyr Asp Thr Ala
                325                 330                 335

Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser Gln Thr Cys Asp Thr
            340                 345                 350

Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser Cys
        355                 360                 365

Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala His
    370                 375                 380

Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys Gln Cys
385                 390                 395                 400

Ala Ser Leu Asn Gly Val Asn Gln Asp Ser His Met Met Ala Ser Met
                405                 410                 415

Leu Ser Asn Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala Tyr
            420                 425                 430

Met Ile Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met Asp
        435                 440                 445

Lys Pro Gln Asn Pro Ile Gln Leu Pro Gly Asp Leu Pro Gly Thr Ser
    450                 455                 460

Tyr Asp Ala Asn Arg Gln Cys Gln Phe Thr Phe Gly Glu Asp Ser Lys
465                 470                 475                 480

His Cys Pro Asp Ala Ala Ser Thr Cys Ser Thr Leu Trp Cys Thr Gly
                485                 490                 495

Thr Ser Gly Gly Val Leu Val Cys Gln Thr Lys His Phe Pro Trp Ala
            500                 505                 510

Asp Gly Thr Ser Cys Gly Glu Gly Lys Trp Cys Ile Asn Gly Lys Cys
        515                 520                 525

Val Asn Lys Thr Asp Arg Lys His Phe Asp Thr Pro Phe His Gly Ser
    530                 535                 540

Trp Gly Met Trp Gly Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly
545                 550                 555                 560
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Gly Val Gln Tyr Thr Met Arg Glu Cys Asp Asn Pro Val Pro Lys Asn
565 570 575

Gly Gly Lys Tyr Cys Glu Gly Lys Arg Val Arg Tyr Arg Ser Cys Asn
580 585 590

Leu Glu Asp Cys Pro Asp Asn Asn Gly Lys Thr Phe Arg Glu Glu Gln
595 600 605

Cys Glu Ala His Asn Glu Phe Ser Lys Ala Ser Phe Gly Ser Gly Pro
610 615 620

Ala Val Glu Trp Ile Pro Lys Tyr Ala Gly Val Ser Pro Lys Asp Arg
625 630 635 640

Cys Lys Leu Ile Cys Gln Ala Lys Gly Ile Gly Tyr Phe Phe Val Leu
645 650 655

Gln Pro Lys Val Val Asp Gly Thr Pro Cys Ser Pro Asp Ser Thr Ser
660 665 670

Val Cys Val Gln Gly Gln Cys Val Lys Ala Gly Cys Asp Arg Ile Ile
675 680 685

Asp Ser Lys Lys Lys Phe Asp Lys Cys Gly Val Cys Gly Gly Asn Gly
690 695 700

Ser Thr Cys Lys Lys Ile Ser Gly Ser Val Thr Ser Ala Lys Pro Gly
705 710 715 720

Tyr His Asp Ile Ile Thr Ile Pro Thr Gly Ala Thr Asn Ile Glu Val
725 730 735

Lys Gln Arg Asn Gln Arg Gly Ser Arg Asn Asn Gly Ser Phe Leu Ala
740 745 750

Ile Lys Ala Ala Asp Gly Thr Tyr Ile Leu Asn Gly Asp Tyr Thr Leu
755 760 765

Ser Thr Leu Glu Gln Asp Ile Met Tyr Lys Gly Val Val Leu Arg Tyr
770 775 780

Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg Ser Phe Ser Pro Leu
785 790 795 800

Lys Glu Pro Leu Thr Ile Gln Val Leu Thr Val Gly Asn Ala Leu Arg
805 810 815

Pro Lys Ile Lys Tyr Thr Tyr Phe Val Lys Lys Lys Lys Glu Ser Phe
820 825 830

Asn Ala Ile Pro Thr Phe Ser Ala Trp Val Ile Glu Glu Trp Gly Glu
835 840 845

Cys Ser Lys Ser Cys Glu Leu Gly Trp Gln Arg Arg Leu Val Glu Cys
850 855 860

Arg Asp Ile Asn Gly Gln Pro Ala Ser Glu Cys Ala Lys Glu Val Lys
865 870 875 880

Pro Ala Ser Thr Arg Pro Cys Ala Asp His Pro Cys Pro Gln Trp Gln
885 890 895

Leu Gly Glu Trp Ser Ser Cys Ser Lys Thr Cys Gly Lys Gly Tyr Lys
900 905 910

Lys Arg Ser Leu Lys Cys Leu Ser His Asp Gly Gly Val Leu Ser His
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Glu Ser Cys Asp Pro Leu Lys Lys Pro Lys His Phe Ile Asp Phe Cys
930 935 940

Thr Met Ala Glu Cys Ser
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Met Phe Pro Ala Pro Ala Ala Pro Arg Trp Leu Pro Phe Leu Leu Leu
 1               5                  10                  15

ctg ctg ctg ctg ctg ctg ccg ctg gcc cgc ggc gcc ccg gcc cgg ccc   96
Leu Leu Leu Leu Leu Leu Pro Leu Ala Arg Gly Ala Pro Ala Arg Pro
            20                  25                  30

gca gcc ggg ggg cag gcc tcg gag ctg gtg gtg ccc acg cgg ttg ccc   144
Ala Ala Gly Gly Gln Ala Ser Glu Leu Val Val Pro Thr Arg Leu Pro
        35                  40                  45

ggc agc gcg ggc gag ctc gcg ctc cac ctg tcc gcc ttc ggc aag ggc   192
Gly Ser Ala Gly Glu Leu Ala Leu His Leu Ser Ala Phe Gly Lys Gly
    50                  55                  60

ttc gtg ttg cgc ctg gcg ccc gac gac agc ttc ctg gcg ccc gag ttc   240
Phe Val Leu Arg Leu Ala Pro Asp Asp Ser Phe Leu Ala Pro Glu Phe
65                  70                  75                  80

aag atc gag cgc ctc ggg ggc tcc ggc cgg gcg acc ggg ggc gag cgg   288
Lys Ile Glu Arg Leu Gly Gly Ser Gly Arg Ala Thr Gly Gly Glu Arg
                85                  90                  95

ggg ctg cgc ggc tgt ttt ttt tcc ggc acc gtg aat ggg gag ccc gag   336
Gly Leu Arg Gly Cys Phe Phe Ser Gly Thr Val Asn Gly Glu Pro Glu
            100                 105                 110

tcg ctg gcg gcg gtc agc ctg tgc cgc ggg ctg agc ggc tcc ttc ctg   384
Ser Leu Ala Ala Val Ser Leu Cys Arg Gly Leu Ser Gly Ser Phe Leu
        115                 120                 125

ctg gac ggc gag gag ttc acc atc cag ccg cag ggc gcg ggg ggc tcc   432
Leu Asp Gly Glu Glu Phe Thr Ile Gln Pro Gln Gly Ala Gly Gly Ser
    130                 135                 140

ctg gct cag ccg cac cgc ctg cag cgc tgg ggt ccc gcc gga gcc cgc   480
Leu Ala Gln Pro His Arg Leu Gln Arg Trp Gly Pro Ala Gly Ala Arg
145                 150                 155                 160

ccc ctc ccg cga gga ccc gag tgg gag gtg gag acg gga gag ggt cag   528
Pro Leu Pro Arg Gly Pro Glu Trp Glu Val Glu Thr Gly Glu Gly Gln
                165                 170                 175

agg cag gag aga gga gac cac cag gag gac agc gag gag gag agc caa   576
Arg Gln Glu Arg Gly Asp His Gln Glu Asp Ser Glu Glu Glu Ser Gln
            180                 185                 190

gaa gag gag gca gaa ggc gct agc gag ccg cca ccg ccc ctg ggg gcc   624
Glu Glu Glu Ala Glu Gly Ala Ser Glu Pro Pro Pro Pro Leu Gly Ala
        195                 200                 205
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acg agt agg acc aag cgg ttt gtg tct gag gcg cgc ttc gtg gag acg   672
Thr Ser Arg Thr Lys Arg Phe Val Ser Glu Ala Arg Phe Val Glu Thr
    210                 215                 220

ctg ctg gtg gcc gat gcg tcc atg gct gcc ttc tac ggg gcc gac ctg   720
Leu Leu Val Ala Asp Ala Ser Met Ala Ala Phe Tyr Gly Ala Asp Leu
225                 230                 235                 240

cag aac cac atc ctg acg tta atg tct gtg gca gcc cga atc tac aag   768
Gln Asn His Ile Leu Thr Leu Met Ser Val Ala Ala Arg Ile Tyr Lys
                245                 250                 255

cac ccc agc atc aag aat tcc atc aac ctg atg gtg gta aaa gtg ctg   816
His Pro Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu
            260                 265                 270

atc gta gaa gat gaa aaa tgg ggc cca gag gtg tcc gac aat ggg ggg   864
Ile Val Glu Asp Glu Lys Trp Gly Pro Glu Val Ser Asp Asn Gly Gly
        275                 280                 285

ctt aca ctg cgt aac ttc tgc aac tgg cag cgg cgt ttc aac cag ccc   912
Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln Arg Arg Phe Asn Gln Pro
    290                 295                 300

agc gac cgc cac cca gag cac tac gac acg gcc atc ctg ctc acc aga   960
Ser Asp Arg His Pro Glu His Tyr Asp Thr Ala Ile Leu Leu Thr Arg
305                 310                 315                 320

cag aac ttc tgt ggg cag gag ggg ctg tgt gac acc ctg ggt gtg gca  1008
Gln Asn Phe Cys Gly Gln Glu Gly Leu Cys Asp Thr Leu Gly Val Ala
                325                 330                 335

gac atc ggg acc att tgt gac ccc aac aaa agc tgc tcc gtg atc gag  1056
Asp Ile Gly Thr Ile Cys Asp Pro Asn Lys Ser Cys Ser Val Ile Glu
            340                 345                 350

gat gag ggg ctc cag gcg gcc cac acc ctg gcc cat gaa cta ggg cac  1104
Asp Glu Gly Leu Gln Ala Ala His Thr Leu Ala His Glu Leu Gly His
        355                 360                 365

gtc ctc agc atg ccc cac gac gac tcc aag ccc tgc aca cgg ctc ttc  1152
Val Leu Ser Met Pro His Asp Asp Ser Lys Pro Cys Thr Arg Leu Phe
    370                 375                 380

ggg ccc atg ggc aag cac cac gtg atg gca ccg ctg ttc gtc cac ctg  1200
Gly Pro Met Gly Lys His His Val Met Ala Pro Leu Phe Val His Leu
385                 390                 395                 400

aac cag acg ctg ccc tgg tcc ccc tgc agc gcc atg tat ctc aca gag  1248
Asn Gln Thr Leu Pro Trp Ser Pro Cys Ser Ala Met Tyr Leu Thr Glu
                405                 410                 415
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```
ctt ctg gac ggc ggg cac gga gac tgt ctc ctg gat gcc cct ggt gcg   1296
Leu Leu Asp Gly Gly His Gly Asp Cys Leu Leu Asp Ala Pro Gly Ala
            420                 425                 430

gcc ctg ccc ctc ccc aca ggc ctc ccg ggc cgc atg gcc ctg tac cag   1344
Ala Leu Pro Leu Pro Thr Gly Leu Pro Gly Arg Met Ala Leu Tyr Gln
        435                 440                 445

ctg gac cag cag tgc agg cag atc ttt ggg ccg gat ttc cgc cac tgc   1392
Leu Asp Gln Gln Cys Arg Gln Ile Phe Gly Pro Asp Phe Arg His Cys
    450                 455                 460

ccc aac acc tct gct cag gac gtc tgc gcc cag ctt tgg tgc cac act   1440
Pro Asn Thr Ser Ala Gln Asp Val Cys Ala Gln Leu Trp Cys His Thr
465                 470                 475                 480

gat ggg gct gag ccc ctg tgc cac acg aag aat ggc agc ctg ccc tgg   1488
Asp Gly Ala Glu Pro Leu Cys His Thr Lys Asn Gly Ser Leu Pro Trp
                485                 490                 495

gct gac ggc acg ccg tgc ggg cct ggg cac ctc tgc tca gaa ggc agc   1536
Ala Asp Gly Thr Pro Cys Gly Pro Gly His Leu Cys Ser Glu Gly Ser
            500                 505                 510

tgt cta cct gag gag gaa gtg gag agg ccc aag ccc gtg gta gat gga   1584
Cys Leu Pro Glu Glu Glu Val Glu Arg Pro Lys Pro Val Val Asp Gly
        515                 520                 525

ggc tgg gca ccg tgg gga ccc tgg gga gaa tgt tct cgg acc tgt gga   1632
Gly Trp Ala Pro Trp Gly Pro Trp Gly Glu Cys Ser Arg Thr Cys Gly
    530                 535                 540

gga gga gta cag ttt tca cac cgt gag tgc aag gac ccc gag cct cag   1680
Gly Gly Val Gln Phe Ser His Arg Glu Cys Lys Asp Pro Glu Pro Gln
545                 550                 555                 560

aat gga gga aga tac tgc ctg ggt cgg aga gcc aag tac cag tca tgc   1728
Asn Gly Gly Arg Tyr Cys Leu Gly Arg Arg Ala Lys Tyr Gln Ser Cys
                565                 570                 575

cac acg gag gaa tgc ccc cct gac ggg aaa agc ttc agg gag cag cag   1776
His Thr Glu Glu Cys Pro Pro Asp Gly Lys Ser Phe Arg Glu Gln Gln
            580                 585                 590

tgt gag aag tat aat gcc tac aat tac act gac atg gac ggg aat ctc   1824
Cys Glu Lys Tyr Asn Ala Tyr Asn Tyr Thr Asp Met Asp Gly Asn Leu
        595                 600                 605

ctg cag tgg gtc ccc aag tat gct ggg gtg tcc ccc cgg gac cgc tgc   1872
Leu Gln Trp Val Pro Lys Tyr Ala Gly Val Ser Pro Arg Asp Arg Cys
    610                 615                 620
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aag ttg ttc tgc cga gcc cgg ggg agg agc gag ttc aaa gtg ttc gag   1920
Lys Leu Phe Cys Arg Ala Arg Gly Arg Ser Glu Phe Lys Val Phe Glu
625                 630                 635                 640

gcc aag gtg att gat ggc acc ctg tgt ggg cca gaa aca ctg gcc atc   1968
Ala Lys Val Ile Asp Gly Thr Leu Cys Gly Pro Glu Thr Leu Ala Ile
                645                 650                 655

tgt gtc cgt ggc cag tgt gtc aag gcc ggc tgt gac cat gtg gtg gac   2016
Cys Val Arg Gly Gln Cys Val Lys Ala Gly Cys Asp His Val Val Asp
            660                 665                 670

tcg cct cgg aag ctg gac aaa tgc ggg gtg tgt ggg ggc aaa ggc aac   2064
Ser Pro Arg Lys Leu Asp Lys Cys Gly Val Cys Gly Gly Lys Gly Asn
        675                 680                 685

tcc tgc agg aag gtc tcc ggg tcc ctc acc ccc acc aat tat ggc tac   2112
Ser Cys Arg Lys Val Ser Gly Ser Leu Thr Pro Thr Asn Tyr Gly Tyr
    690                 695                 700

aat gac att gtc acc atc cca gct ggt gcc act aat att gac gtg aag   2160
Asn Asp Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Lys
705                 710                 715                 720

cag cgg agc cac ccg ggt gtg cag aac gat ggg aac tac ctg gcg ctg   2208
Gln Arg Ser His Pro Gly Val Gln Asn Asp Gly Asn Tyr Leu Ala Leu
                725                 730                 735

aag acg gct gat ggg cag tac ctg ctc aac ggc aac ctg gcc atc tct   2256
Lys Thr Ala Asp Gly Gln Tyr Leu Leu Asn Gly Asn Leu Ala Ile Ser
            740                 745                 750

gcc ata gag cag gac atc ttg gtg aag ggg acc atc ctg aag tac agc   2304
Ala Ile Glu Gln Asp Ile Leu Val Lys Gly Thr Ile Leu Lys Tyr Ser
        755                 760                 765

ggc tcc atc gcc acc ctg gag cgc ctg cag agc ttc cgg ccc ttg cca   2352
Gly Ser Ile Ala Thr Leu Glu Arg Leu Gln Ser Phe Arg Pro Leu Pro
    770                 775                 780

gag cct ctg aca gtg cag ctc ctg aca gtc cct ggc gag gtc ttc ccc   2400
Glu Pro Leu Thr Val Gln Leu Leu Thr Val Pro Gly Glu Val Phe Pro
785                 790                 795                 800

cca aaa gtc aaa tac acc ttc ttt gtt cct aat gac gtg gac ttt agc   2448
Pro Lys Val Lys Tyr Thr Phe Phe Val Pro Asn Asp Val Asp Phe Ser
                805                 810                 815

atg cag agc agc aaa gag aga gca acc acc aac atc atc cag ccg ctg   2496
Met Gln Ser Ser Lys Glu Arg Ala Thr Thr Asn Ile Ile Gln Pro Leu
            820                 825                 830
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ctc cac gca cag tgg gtg ctg ggg gac tgg tct gag tgc tct agc acc 2544
Leu His Ala Gln Trp Val Leu Gly Asp Trp Ser Glu Cys Ser Ser Thr
835 840 845

tgc ggg gcc ggc tgg cag agg cga act gta gag tgc agg gac ccc tcc 2592
Cys Gly Ala Gly Trp Gln Arg Arg Thr Val Glu Cys Arg Asp Pro Ser
850 855 860

ggc cag gcc tct gcc acc tgc aac aag gct ctg aaa ccc gag gat gcc 2640
Gly Gln Ala Ser Ala Thr Cys Asn Lys Ala Leu Lys Pro Glu Asp Ala
865 870 875 880

aag ccc tgc gaa agc cag ctg tgc ccc ctg tgattcaggg gggcaggggc 2690
Lys Pro Cys Glu Ser Gln Leu Cys Pro Leu
885 890

cagtcttgtg ctcctggaca tgcggtactg aggtgcagac aaggtctcca ctgtggtgac 2750

tgggtccctt ggccatatca aggcagcacg gcccacccag gcctcccatt gccgcaaccc 2810

ctccagtact gcacaaattc ctaaggggga agagaaaagg tatggggcgg caaaacctat 2870

catcaactgt ccawtgnaat ggaacttgct cgggttcaat taaaggcata agttaaagta 2930

aattcattat gatcaacaga cctcacntca tctgttgcan gatacaacta ntaaaaaaaa 2990

aaaaaaaaaa aaaaaaaa 3008

<210> 4
<211> 890
<212> PRT
<213> Homo sapiens

<400> 4
Met Phe Pro Ala Pro Ala Ala Pro Arg Trp Leu Pro Phe Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Pro Leu Ala Arg Gly Ala Pro Ala Arg Pro
20 25 30

Ala Ala Gly Gly Gln Ala Ser Glu Leu Val Val Pro Thr Arg Leu Pro
35 40 45

Gly Ser Ala Gly Glu Leu Ala Leu His Leu Ser Ala Phe Gly Lys Gly
50 55 60

Phe Val Leu Arg Leu Ala Pro Asp Asp Ser Phe Leu Ala Pro Glu Phe
65 70 75 80

Lys Ile Glu Arg Leu Gly Gly Ser Gly Arg Ala Thr Gly Gly Glu Arg

85 90 95

Gly Leu Arg Gly Cys Phe Phe Ser Gly Thr Val Asn Gly Glu Pro Glu
100 105 110

Ser Leu Ala Ala Val Ser Leu Cys Arg Gly Leu Ser Gly Ser Phe Leu
115 120 125

Leu Asp Gly Glu Glu Phe Thr Ile Gln Pro Gln Gly Ala Gly Gly Ser
130 135 140

Leu Ala Gln Pro His Arg Leu Gln Arg Trp Gly Pro Ala Gly Ala Arg
145 150 155 160

Pro Leu Pro Arg Gly Pro Glu Trp Glu Val Glu Thr Gly Glu Gly Gln
165 170 175

Arg Gln Glu Arg Gly Asp His Gln Glu Asp Ser Glu Glu Glu Ser Gln
180 185 190

Glu Glu Glu Ala Glu Gly Ala Ser Glu Pro Pro Pro Pro Leu Gly Ala
195 200 205

Thr Ser Arg Thr Lys Arg Phe Val Ser Glu Ala Arg Phe Val Glu Thr
210 215 220

Leu Leu Val Ala Asp Ala Ser Met Ala Ala Phe Tyr Gly Ala Asp Leu
225 230 235 240

Gln Asn His Ile Leu Thr Leu Met Ser Val Ala Ala Arg Ile Tyr Lys
245 250 255

His Pro Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu
260 265 270

Ile Val Glu Asp Glu Lys Trp Gly Pro Glu Val Ser Asp Asn Gly Gly
275 280 285

Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln Arg Arg Phe Asn Gln Pro
290 295 300

Ser Asp Arg His Pro Glu His Tyr Asp Thr Ala Ile Leu Leu Thr Arg
305 310 315 320

Gln Asn Phe Cys Gly Gln Glu Gly Leu Cys Asp Thr Leu Gly Val Ala
325 330 335

Asp Ile Gly Thr Ile Cys Asp Pro Asn Lys Ser Cys Ser Val Ile Glu
340 345 350

Asp Glu Gly Leu Gln Ala Ala His Thr Leu Ala His Glu Leu Gly His
355 360 365

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Val Leu Ser Met Pro His Asp Asp Ser Lys Pro Cys Thr Arg Leu Phe
    370                 375                 380

Gly Pro Met Gly Lys His His Val Met Ala Pro Leu Phe Val His Leu
385                 390                 395                 400

Asn Gln Thr Leu Pro Trp Ser Pro Cys Ser Ala Met Tyr Leu Thr Glu
                405                 410                 415

Leu Leu Asp Gly Gly His Gly Asp Cys Leu Leu Asp Ala Pro Gly Ala
            420                 425                 430

Ala Leu Pro Leu Pro Thr Gly Leu Pro Gly Arg Met Ala Leu Tyr Gln
        435                 440                 445

Leu Asp Gln Gln Cys Arg Gln Ile Phe Gly Pro Asp Phe Arg His Cys
    450                 455                 460

Pro Asn Thr Ser Ala Gln Asp Val Cys Ala Gln Leu Trp Cys His Thr
465                 470                 475                 480

Asp Gly Ala Glu Pro Leu Cys His Thr Lys Asn Gly Ser Leu Pro Trp
                485                 490                 495

Ala Asp Gly Thr Pro Cys Gly Pro Gly His Leu Cys Ser Glu Gly Ser
            500                 505                 510

Cys Leu Pro Glu Glu Glu Val Glu Arg Pro Lys Pro Val Val Asp Gly
        515                 520                 525

Gly Trp Ala Pro Trp Gly Pro Trp Gly Glu Cys Ser Arg Thr Cys Gly
    530                 535                 540

Gly Gly Val Gln Phe Ser His Arg Glu Cys Lys Asp Pro Glu Pro Gln
545                 550                 555                 560

Asn Gly Gly Arg Tyr Cys Leu Gly Arg Arg Ala Lys Tyr Gln Ser Cys
                565                 570                 575

His Thr Glu Glu Cys Pro Pro Asp Gly Lys Ser Phe Arg Glu Gln Gln
            580                 585                 590

Cys Glu Lys Tyr Asn Ala Tyr Asn Tyr Thr Asp Met Asp Gly Asn Leu
        595                 600                 605

Leu Gln Trp Val Pro Lys Tyr Ala Gly Val Ser Pro Arg Asp Arg Cys
    610                 615                 620

Lys Leu Phe Cys Arg Ala Arg Gly Arg Ser Glu Phe Lys Val Phe Glu
625                 630                 635                 640
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Ala Lys Val Ile Asp Gly Thr Leu Cys Gly Pro Glu Thr Leu Ala Ile
                645                 650                 655

Cys Val Arg Gly Gln Cys Val Lys Ala Gly Cys Asp His Val Val Asp
            660                 665                 670

Ser Pro Arg Lys Leu Asp Lys Cys Gly Val Cys Gly Gly Lys Gly Asn
        675                 680                 685

Ser Cys Arg Lys Val Ser Gly Ser Leu Thr Pro Thr Asn Tyr Gly Tyr
    690                 695                 700

Asn Asp Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Lys
705                 710                 715                 720

Gln Arg Ser His Pro Gly Val Gln Asn Asp Gly Asn Tyr Leu Ala Leu
                725                 730                 735

Lys Thr Ala Asp Gly Gln Tyr Leu Leu Asn Gly Asn Leu Ala Ile Ser
            740                 745                 750

Ala Ile Glu Gln Asp Ile Leu Val Lys Gly Thr Ile Leu Lys Tyr Ser
        755                 760                 765

Gly Ser Ile Ala Thr Leu Glu Arg Leu Gln Ser Phe Arg Pro Leu Pro
    770                 775                 780

Glu Pro Leu Thr Val Gln Leu Leu Thr Val Pro Gly Glu Val Phe Pro
785                 790                 795                 800

Pro Lys Val Lys Tyr Thr Phe Phe Val Pro Asn Asp Val Asp Phe Ser
                805                 810                 815

Met Gln Ser Ser Lys Glu Arg Ala Thr Thr Asn Ile Ile Gln Pro Leu
            820                 825                 830

Leu His Ala Gln Trp Val Leu Gly Asp Trp Ser Glu Cys Ser Ser Thr
        835                 840                 845

Cys Gly Ala Gly Trp Gln Arg Arg Thr Val Glu Cys Arg Asp Pro Ser
    850                 855                 860

Gly Gln Ala Ser Ala Thr Cys Asn Lys Ala Leu Lys Pro Glu Asp Ala
865                 870                 875                 880

Lys Pro Cys Glu Ser Gln Leu Cys Pro Leu
                885                 890
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<211> 1203
<212> PRT

<213> Bovine

<400> 5

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Leu Leu Leu Leu Leu Leu Pro Leu Pro Ala Asp Ala Arg Leu Ala Ala
            20                  25                  30

Ala Ala Ala Asp Pro Pro Gly Gly Pro Gln Gly His Gly Ala Glu Arg
        35                  40                  45

Ile Leu Ala Val Pro Val Arg Thr Asp Ala Gln Gly Arg Leu Val Ser
    50                  55                  60

His Val Val Ser Ala Ala Thr Ala Pro Ala Gly Val Arg Thr Arg Arg
65                  70                  75                  80

Ala Ala Pro Ala Gln Ile Pro Gly Leu Ser Gly Gly Ser Glu Glu Asp
                85                  90                  95

Pro Gly Gly Arg Leu Phe Tyr Asn Val Thr Val Phe Gly Arg Asp Leu
            100                 105                 110

His Leu Arg Leu Arg Pro Asn Ala Arg Leu Val Ala Pro Gly Ala Thr
        115                 120                 125

Val Glu Trp Gln Gly Glu Ser Gly Ala Thr Arg Val Glu Pro Leu Leu
    130                 135                 140

Gly Thr Cys Leu Tyr Val Gly Asp Val Ala Gly Leu Ala Glu Ser Ser
145                 150                 155                 160

Ser Val Ala Leu Ser Asn Cys Asp Gly Leu Ala Gly Leu Ile Arg Met
                165                 170                 175

Glu Glu Glu Glu Phe Phe Ile Glu Pro Leu Glu Lys Gly Leu Ala Ala
            180                 185                 190

Lys Glu Ala Glu Gln Gly Arg Val His Val Val Tyr His Arg Pro Thr
        195                 200                 205

Thr Ser Arg Pro Pro Pro Leu Gly Gln Ala Leu Asp Thr Gly Ile Ser
    210                 215                 220

Ala Asp Ser Leu Asp Ser Leu Ser Arg Ala Leu Gly Val Leu Glu Glu
225                 230                 235                 240

Arg Val Asn Ser Ser Arg Arg Arg Met Arg Arg His Ala Ala Asp Asp
                245                 250                 255

Asp Tyr Asn Ile Glu Val Leu Leu Gly Val Asp Asp Ser Val Val Gln
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260 265 270

Phe His Gly Thr Glu His Val Gln Lys Tyr Leu Leu Thr Leu Met Asn
275 280 285

Ile Val Asn Glu Ile Tyr His Asp Glu Ser Leu Gly Ala His Ile Asn
290 295 300

Val Val Leu Val Arg Ile Ile Leu Leu Ser Tyr Gly Lys Ser Met Ser
305 310 315 320

Leu Ile Glu Ile Gly Asn Pro Ser Gln Ser Leu Glu Asn Val Cys Arg
325 330 335

Trp Ala Tyr Leu Gln Gln Lys Pro Asp Thr Asp His Asp Glu Tyr His
340 345 350

Asp His Ala Ile Phe Leu Thr Arg Gln Asp Phe Gly Pro Ser Gly Met
355 360 365

Gln Gly Tyr Ala Pro Val Thr Gly Met Cys His Pro Val Arg Ser Cys
370 375 380

Thr Leu Asn His Glu Asp Gly Phe Ser Ser Ala Phe Val Val Ala His
385 390 395 400

Glu Thr Gly His Val Leu Gly Met Glu His Asp Gly Gln Gly Asn Arg
405 410 415

Cys Gly Asp Glu Val Arg Leu Gly Ser Ile Met Ala Pro Leu Val Gln
420 425 430

Ala Ala Phe His Arg Phe His Trp Ser Arg Cys Ser Gln Gln Glu Leu
435 440 445

Ser Arg Tyr Leu His Ser Tyr Asp Cys Leu Arg Asp Asp Pro Phe Thr
450 455 460

His Asp Trp Pro Ala Leu Pro Gln Leu Pro Gly Leu His Tyr Ser Met
465 470 475 480

Asn Glu Gln Cys Arg Phe Asp Phe Gly Leu Gly Tyr Met Met Cys Thr
485 490 495

Ala Phe Arg Thr Phe Asp Pro Cys Lys Gln Leu Trp Cys Ser His Pro
500 505 510

Asp Asn Pro Tyr Phe Cys Lys Thr Lys Lys Gly Pro Pro Leu Asp Gly
515 520 525

Thr Met Cys Ala Pro Gly Lys His Cys Phe Lys Gly His Cys Ile Trp
530 535 540

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Leu Thr Pro Asp Ile Leu Lys Arg Asp Gly Asn Trp Gly Ala Trp Ser
545                 550                 555                 560

Pro Phe Gly Ser Cys Ser Arg Thr Cys Gly Thr Gly Val Lys Phe Arg
                565                 570                 575

Thr Arg Gln Cys Asp Asn Pro His Pro Ala Asn Gly Gly Arg Thr Cys
            580                 585                 590

Ser Gly Leu Ala Tyr Asp Phe Gln Leu Cys Asn Ser Gln Asp Cys Pro
        595                 600                 605

Asp Ala Leu Ala Asp Phe Arg Glu Glu Gln Cys Arg Gln Trp Asp Leu
    610                 615                 620

Tyr Phe Glu His Gly Asp Ala Gln His His Trp Leu Pro His Glu His
625                 630                 635                 640

Arg Asp Ala Lys Glu Arg Cys His Leu Tyr Cys Glu Ser Lys Glu Thr
                645                 650                 655

Gly Glu Val Val Ser Met Lys Arg Met Val His Asp Gly Thr Arg Cys
            660                 665                 670

Ser Tyr Lys Asp Ala Phe Ser Leu Cys Val Arg Gly Asp Cys Arg Lys
        675                 680                 685

Val Gly Cys Asp Gly Val Ile Gly Ser Ser Lys Gln Glu Asp Lys Cys
    690                 695                 700

Gly Val Cys Gly Gly Asp Asn Ser His Cys Lys Val Val Lys Gly Thr
705                 710                 715                 720

Phe Ser Arg Ser Pro Lys Lys Leu Gly Tyr Ile Lys Met Phe Glu Ile
                725                 730                 735

Pro Ala Gly Ala Arg His Leu Leu Ile Gln Glu Ala Asp Thr Thr Ser
            740                 745                 750

His His Leu Ala Val Lys Asn Leu Glu Thr Gly Lys Phe Ile Leu Asn
        755                 760                 765

Glu Glu Asn Asp Val Asp Pro Asn Ser Lys Thr Phe Ile Ala Met Gly
    770                 775                 780

Val Glu Trp Glu Tyr Arg Asp Glu Asp Gly Arg Glu Thr Leu Gln Thr
785                 790                 795                 800

Met Gly Pro Leu His Gly Thr Ile Thr Val Leu Val Ile Pro Glu Gly
                805                 810                 815
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Asp Ala Arg Ile Ser Leu Thr Tyr Lys Tyr Met Ile His Glu Asp Ser
820 825 830

Leu Asn Val Asp Asp Asn Asn Val Leu Glu Asp Asp Ser Val Gly Tyr
835 840 845

Glu Trp Ala Leu Lys Lys Trp Ser Pro Cys Ser Lys Pro Cys Gly Gly
850 855 860

Gly Ser Gln Phe Thr Lys Tyr Gly Cys Arg Arg Arg Leu Asp His Lys
865 870 875 880

Met Val His Arg Gly Phe Cys Asp Ser Val Ser Lys Pro Lys Ala Ile
885 890 895

Arg Arg Thr Cys Asn Pro Gln Glu Cys Ser Gln Pro Val Trp Val Thr
900 905 910

Gly Glu Trp Glu Pro Cys Ser Arg Ser Cys Gly Arg Thr Gly Met Gln
915 920 925

Val Arg Ser Val Arg Cys Val Gln Pro Leu His Asn Asn Thr Thr Arg
930 935 940

Ser Val His Thr Lys His Cys Asn Asp Ala Arg Pro Glu Gly Arg Arg
945 950 955 960

Ala Cys Asn Arg Glu Leu Cys Pro Gly Arg Trp Arg Ala Gly Ser Trp
965 970 975

Ser Gln Cys Ser Val Thr Cys Gly Asn Gly Thr Gln Glu Arg Pro Val
980 985 990

Leu Cys Arg Thr Ala Asp Asp Ser Phe Gly Val Cys Arg Glu Glu Arg
995 1000 1005

Pro Glu Thr Ala Arg Ile Cys Arg Leu Gly Pro Cys Pro Arg Asn Thr
1010 1015 1020

Ser Asp Pro Ser Lys Lys Ser Tyr Val Val Gln Trp Leu Ser Arg Pro
1025 1030 1035 1040

Asp Pro Asn Ser Pro Val Gln Glu Thr Ser Ser Lys Gly Arg Cys Gln
1045 1050 1055

Gly Asp Lys Ser Val Phe Cys Arg Met Glu Val Leu Ser Arg Tyr Cys
1060 1065 1070

Ser Ile Pro Gly Tyr Asn Lys Leu Cys Cys Lys Ser Cys Asn Pro His
1075 1080 1085

Asp Asn Leu Thr Asp Val Asp Asp Arg Ala Glu Pro Pro Ser Gly Lys

1090 1095 1100

His Asn Asp Ile Glu Glu Leu Met Pro Thr Leu Ser Val Pro Thr Leu
1105 1110 1115 1120

Val Met Glu Val Gln Pro Pro Pro Gly Ile Pro Leu Glu Val Pro Leu
1125 1130 1135

Asn Thr Ser Ser Thr Asn Ala Thr Glu Asp His Pro Glu Thr Asn Ala
1140 1145 1150

Val Asp Val Pro Tyr Lys Ile Pro Gly Leu Glu Asp Glu Val Gln Pro
1155 1160 1165

Pro Asn Leu Ile Pro Arg Arg Pro Ser Pro Tyr Glu Lys Thr Arg Asn
1170 1175 1180

Gln Arg Ile Gln Glu Leu Ile Asp Glu Met Arg Lys Lys Glu Met Leu
1185 1190 1195 1200

Gly Lys Phe

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<211> 50
<212> PRT
<213> Homo sapiens

<400> 6
Asp Asp Gly Trp Ser Pro Trp Ser Glu Trp Thr Ser Cys Ser Thr Ser
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Cys Gly Asn Gly Ile Gln Gln Arg Gly Arg Ser Cys Asp Ser Leu Asn
20 25 30

Asn Arg Cys Glu Gly Ser Ser Val Gln Thr Arg Thr Cys His Ile Gln
35 40 45

Glu Cys
50

<210> 7
<211> 57
<212> PRT
<213> Homo sapiens

<400> 7
Asp Gly Gly Trp Ser His Trp Ser Pro Trp Ser Ser Cys Ser Val Thr
1 5 10 15

Cys Gly Asp Gly Val Ile Thr Arg Ile Arg Leu Cys Asn Ser Pro Ser
20 25 30

Pro Gln Met Asn Gly Lys Pro Cys Glu Gly Glu Ala Arg Glu Thr Lys
35 40 45

Ala Cys Lys Lys Asp Ala Cys Pro Ile
50 55

<210> 8
<211> 57
<212> PRT
<213> Homo sapiens

<400> 8
Asn Gly Gly Trp Gly Pro Trp Ser Pro Trp Asp Ile Cys Ser Val Thr
1 5 10 15

Cys Gly Gly Gly Val Gln Lys Arg Ser Arg Leu Cys Asn Asn Pro Thr
20 25 30

Pro Gln Phe Gly Gly Lys Asp Cys Val Gly Asp Val Thr Glu Asn Gln
35 40 45

Ile Cys Asn Lys Gln Asp Cys Pro Ile
50 55

<210> 9
<211> 50
<212> PRT
<213> Homo sapiens

<400> 9
Glu Glu Gly Trp Ser Pro Trp Ala Glu Trp Thr Gln Cys Ser Val Thr
1 5 10 15

Cys Gly Ser Gly Thr Gln Gln Arg Gly Arg Ser Cys Asp Val Thr Ser
20 25 30

Asn Thr Cys Leu Gly Pro Ser Ile Gln Thr Arg Ala Cys Ser Leu Ser
35 40 45

Lys Cys
50

<210> 10
<211> 57
<212> PRT
<213> Homo sapiens

<400> 10
Asp Gly Gly Trp Ser His Trp Ser Pro Trp Ser Ser Cys Ser Val Thr
1 5 10 15

Cys Gly Val Gly Asn Ile Thr Arg Ile Arg Leu Cys Asn Ser Pro Val
20 25 30

Pro Gln Met Gly Gly Lys Asn Cys Lys Gly Ser Gly Arg Glu Thr Lys
35 40 45

Ala Cys Gln Gly Ala Pro Cys Pro Ile
50 55

<210> 11
<211> 56
<212> PRT
<213> Homo sapiens

<400> 11
Asp Gly Arg Trp Ser Pro Trp Ser Pro Trp Ser Ala Cys Thr Val Thr
1 5 10 15

Cys Ala Gly Gly Ile Arg Glu Arg Thr Arg Val Cys Asn Ser Pro Glu
20 25 30

Pro Gln Tyr Gly Gly Lys Ala Cys Val Gly Asp Val Gln Glu Arg Gln
35 40 45

Met Cys Asn Lys Arg Ser Cys Pro
50 55

<210> 12
<211> 3974
<212> DNA
<213> Homo sapiens

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ccggaagcat aaagtgtaaa gcctggggtg cctaatgagt gagctaactc acattaattg 180

cgttgcgctc actgcccgct ttccagtcgg gaaacctgtc gtgccagctg cattaatgaa 240

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taatacggtt atccacagaa tcaggggata acgcaggaaa gaacatgtga gcaaaaggcc 420

agcaaaaggc caggaaccgt aaaaaggccg cgttgctggc gtttttccat aggctccgcc 480

cccctgacga gcatcacaaa aatcgacgct caagtcagag gtggcgaaac ccgacaggac 540

tataaagata ccaggcgttt cccccctggaa gctccctcgt gcgctctcct gttccgaccc 600

tgccgcttac cggatacctg tccgcctttc tcccttcggg aagcgtggcg ctttctcata 660

gctcacgctg taggtatctc agttcggtgt aggtcgttcg ctccaagctg ggctgtgtgc 720

acgaaccccc cgttcagccc gaccgctgcg ccttatccgg taactatcgt cttgagtcca 780

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gaagaacagt atttggtatc tgcgctctgc tgaagccagt taccttcgga aaaagagttg 960

gtagctcttg atccggcaaa caaaccaccg ctggtagcgg tggtttttt gtttgcaagc 1020

agcagattac gcgcagaaaa aaaggatctc aagaagatcc tttgatcttt tctacggggt 1080

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caattcgcgc gcgaaggcga agcggcatgc atttacgttg acaccatcga atggtgcaaa 1200

acctttcgcg gtatggcatg atagcgcccg gaagagagtc aattcagggt ggtgaatgtg 1260

aaaccagtaa cgttatacga tgtcgcagag tatgccggtg tctcttatca gaccgtttcc 1320

cgcgtggtga accaggccag ccacgtttct gcgaaaacgc gggaaaaagt ggaagcggcg 1380

atggcggagc tgaattacat tcccaaccgc gtggcacaac aactggcggg caaacagtcg 1440

ttgctgattg gcgttgccac ctccagtctg gccctgcacg cgccgtcgca aattgtcgcg 1500

gcgattaaat ctcgcgccga tcaactgggt gccagcgtgg tggtgtcgat ggtagaacga 1560

agcggcgtcg aagcctgtaa agcggcggtg cacaatcttc tcgcgcaacg cgtcagtggg 1620

ctgatcatta actatccgct ggatgaccag gatgccattg ctgtggaagc tgcctgcact 1680

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cataaatatc tcactcgcaa tcaaattcag ccgatagcgg aacgggaagg cgactggagt 1920

gccatgtccg gttttcaaca aaccatgcaa atgctgaatg agggcatcgt tcccactgcg 1980

atgctggttg ccaacgatca gatggcgctg ggcgcaatgc gcgccattac cgagtccggg 2040

ctgcgcgttg gtgcggatat ctcggtagtg ggatacgacg ataccgaaga cagctcatgt 2100

tatatcccgc cgttaaccac catcaaacag gattttcgcc tgctggggca aaccagcgtg 2160

gaccgcttgc tgcaactctc tcagggccag gcggtgaagg gcaatcagct gttgcccgtc 2220

tcactggtga aaagaaaaac caccctggcg cccaatacgc aaaccgcctc tccccgcgcg 2280

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gaaccccaga gtcccgctca gaagaactcg tcaagaaggc gatagaaggc gatgcgctgc 2760

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cagcaccgtt tctgcggact ggctttctac gtgttccgct tcctttagca gcccttgcgc 3840

cctgagtgct tgcggcagcg tgaagcttaa aaaactgcaa aaaatagttt gacttgtgag 3900

cggataacaa ttaagatgta cccaattgtg agcggataac aatttcacac attaaagagg 3960

agaaattaca tatg 3974

<210> 13
<211> 112
<212> DNA
<213> Homo sapiens

<400> 13
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caattgtgag cggataacaa tttcacacat taaagaggag aaattacata tg 112

<210> 14
<211> 542
<212> DNA
<213> Mus musculus

<220>
<221> UNSURE
<222> (3)
<223> May be any nucleic acid

<220>
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<222> (21)
<223> May be any nucleic acid

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<222> (22)
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<223> May be any nucleic acid

<220>
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<222> (535)
<223> May be any nucleic acid

<400> 14
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acaacccagt cccaaagaat ggagggaagt actgtgaagg caaacgagtg cgctacagat 180

cctgtaacct tgaggactgt ccagacaata atggaaaaac ctttagagag gaacaatgtg 240

aagcacacaa cgagttttca aaagcttcct ttgggagtgg gcctgcggtg gaatggattc 300

ccaagtacgc tggcgtctca ccaaaggaca ggtgcaagtt catgttgcca agccaaaggc 360

nttggctant tctttcgttt tgcagcccaa ggttgttagg tgggtantcc atgttaggcc 420

cagattncac ctttgtctgt gtgcaaggac agtgtgttaa aagttggttg tgatccgcnt 480

cntagattcc aaaaggagtt ttgttaatgt ggtgttttcn gggggaatgg tctanttta 540

aa 542

<210> 15
<211> 320

<212> DNA
<213> Unknown

<220>
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Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

17. A method for inhibiting angiogenesis in an individual, comprising administering an effective amount of a polypeptide of claim 10 to said individual.

18. A polypeptide comprising the amino acid sequence m-n of SEQ ID NO:2, wherein m is an integer of 1 to 950, and wherein n is an integer of 10 to 950.

19. A polypeptide comprising the amino acid sequence m-n of SEQ ID NO:4, wherein m is an integer of 1 to 890, and wherein n is an integer of 10 to 890.

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CTGGCCGTGTCGGACGCACTCGGGCGCCCCTCCGAGGAGGACGAGGAGCTAGTGGTGCCGGAGCTGGAGCGCGCCCCG
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GGACACGGGACCACGCGCCTCCGCCTGCACGCCTTTGACCAGCAGCTGGATCTGGAGCTGCGGCCCGACAGCAGCTTT
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 L  A  P  G  F  T  L  Q  N  V  G  R  K  S  G  S  E  T  P  L  P  E  T  D  L  A

CACTGCTTCTACTCCGGCACCGTGAATGGCGATCCCAGCTCGGCTGCCGCCCTCAGCCTCTGCGAGGGCGTGCGCGGC
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FIGURE 1

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<211> 2837
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

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<211> 4108
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

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<211> 820
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

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<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

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<211> 4100

<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

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<213> Unknown

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<220>
<223> Description of Unknown Organism:Unknown

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ggcaagggca agttcaacgc ccgcacccgc cgccacctcc gggtgcgcaa gcggatctcc 2760

ggcaccacgt ccgtcccccg cctcgtcgtc aaccgctctg cacggcacat gttcgtgcag 2820

gtcgtggacg acacgcagag ccgcacgatc gcgtacgcct ccaccatgga ggccgacgtg 2880

cgtgcgctcg agggtgacaa gacggccaag gccaagcgcg tgggcgagct cgtcgccgag 2940

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cggccgcggt ggccggacgg cgatcgtcgt ggcggccgtc ggacgaccga accgtcgtgg 3240

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ccaccgagcg ttacctgcag tacgtcatca gccgcatcac gttcgtggtg ggggccctct 5760

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tcgcccgcgt ggacggcacc ggccagatcg acgacgtcac cgagcgcctg ctgcaggccg 6540

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ttcaccaccg cggagctgga cgccgtgttc gcggtggtgc tggccgaacg cggtgcgacc 6780

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<210> 42
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<212> DNA
<213> Homo sapiens

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ttcagcgcca ggtagttccc atcgttctgc acacccgggt ggctccgctg cttcacgtca 120

atattagtgg caccagctgg gatggtgaca atgtcattgt agccataatt ggtgggggtg 180

agggacccgg agaccttcct gcaggagttg nctttgcccc cacacacccc gcatttgtcc 240

agcttccgag gcgagtccac cacatggtca cagccggcct tgacacactg gncacggaca 300

cagatggnca gtgtttctgg cccacacagg gtgccatcaa tcaccttggn ctcgaacact 360

ttggaactcg ctcctccccc gggntcggga ggaacaactt gcaggggtcc cgggggggac 420

aacccagcat tcttggggga cccactgcag gaggattccc cgtccatgtc aagtgtnatt 480

ggtgggcatt attcttctca caattgntgc tccctgaagg ttttcccgnc aaggggggat 540

tcccccccng ntggaatnat tggtacttgg gtctccga 578

<210> 43
<211> 305
<212> DNA
<213> Homo sapiens

<220>
<221> UNSURE
<222> (128)
<223> May be any nucleic acid

<220>
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<222> (146)
<223> May be any nucleic acid

<400> 43
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aagtgcactt ttacctttta acctatgccc tctacttgaa cccgagcaag gtccagtcca 120

ctggacangt tgatgatagg gtctgncgcc ccataccctc tcctcttccc ccttaggaat 180

ttgtgcagta ctggaggggt tgcggcaatg ggaggcctgg gtgggccgtg ctgccttgat 240

atggccaagg gacccagtca ccacagtgga gacccttgtc tgcacctcag taccgcatgt 300

ccagg 305

<210> 44
<211> 333
<212> DNA
<213> Homo sapiens

<220>
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<222> (82)
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<223> May be any nucleic acid

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<222> (324)
<223> May be any nucleic acid

<400> 44
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ccgctgctcc acgcacagtg gntgctgggg gactggtctg agtgctctag cactgcgggg 120

ccggctggca gaggcgaact gtagagtgca gggacccctc cggtgcaggc ctctgccacc 180

tgcaacaagg ctctggaaac ccgaggatgc caagccctgg cagaaccagc tgtgcccccc 240

gtgatttcag ggggncaggg gccattttgt gctcngggac atgcggtaat ggaggttgnc 300

agacaaggtc ttncattgtg gtgnatgggt tcc 333

<210> 45
<211> 102
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<400> 45

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<222> (64)
<223> May be any nucleic acid

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<223> May be any nucleic acid

gcagcagcag cgcagcgcag agagagcagc agcagcagca gcagcagcag cagagcagat 60

cntnctggna nnaaaaaatc gcggcagcag ctgctctagc ag 102

<210> 46
<211> 123
<212> DNA
<213> Unknown

<220>
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<400> 46
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aggggggngcc cgggacccaa ggcgcccgaa cagagaggcg gagcacaatc cactggtcgg 120

cgn 123

<210> 47
<211> 109
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

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<400> 47
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agagagcagc agagcagagc agagcanagt agagnagagc anagcnnac 109

<210> 48
<211> 293
<212> DNA
<213> Homo sapiens

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<222> (185)
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<222> (234)
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<400> 48
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gtccgggccc ggccgggcat ggattnaatg cctgagcccg ggtcccgctg tcttctgctt 120

cttcccttgc tgctgctgct gctgctgctg ctgccggccc cggagntggg cccgagccag 180

gccgnagctg aggagaacga cttgggttng cctncccana aaatgggaag gganttgggg 240

ttaatcgaag tcattgggac cattttaaaa ggggcttcct ggattatagn ctt 293

<210> 49
<211> 506
<212> DNA
<213> Homo sapiens

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<222> (283)
<223> May be any nucleic acid

<220>
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<222> (454)
<223> May be any nucleic acid

<220>
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<400> 49
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gcagcagcag cagcagcagc agcagcaaca gtaacagcag cagttcgtcc ggacccaacc 120

cttctacctc ctttgagccc atcaaggcag accccacagg tgttttggaa ctccccaaag 180

agctgtcaga aatctttgat cccacacgag agtgcatgag ctcggagctg ctggaggagt 240

tgatgtcctc agaagtgttt gcccctctgc tttcgtcttt ctncaccccc gggagaccac 300

gattatatct acaacctgga cgagagtgaa ggtgtttgtg anctcttttg atgtgnctgt 360

tntnaacntt tgactgacag ggacatgcct tttttggttg ggacccagat tttttgactt 420

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ttcggcttcc ttaacgaaag ttttgg 506

<210> 50
<211> 419
<212> DNA
<213> Homo sapiens

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<223> May be any nucleic acid

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tgcatgctct tgtctccctt aatggagaga gtgtgacact gcttagcact tggatggctt 120

ggggtggtgg ttatgancag cagtctgtca cagctcagcg aggtgaagcc tgtgggcgtt 180

ttgctctgtg ctgaatggct cagtggccct acaaagcgga ntcagctctt ggtggctttc 240

tgttgtggtg ggctgctgnt gctgctgctg ctgctgctgc tgctgccctt gcctctaaaa 300

gaactcactt cctcttcctc ctgctgncac ctgtcttttg gcttgtggga ttggagtcat 360

ggggcccaga tggagccttg ctccntgant tatgataggc ccctcggtct cttttntnc 419

<210> 51
<211> 495
<212> DNA
<213> Saccharomyces cerevisiae

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<222> (177)
<223> May be any nucleic acid

<220>
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<222> (322)
<223> May be any nucleic acid

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<223> May be any nucleic acid

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cagaggtgca gctgaaggag gaatctgctg ctgctgctgc tgctgctgcc gcagacnccc 180

agtccctggg actcccacct ccgagccagc tcccaccccc agcatgactg gcctgcctct 240

gtctgctctt ccaccacctc ttgcacaaag cccagtcctc cggcccagaa catcctgggc 300

ccggagttcc ttccttgcct tnaggggntt ttcagcaagt tnagttcctt gggtcctttt 360

tgggaaantt naggnagttn aaggantacc aggttnttgc catnctttcc agatccaagt 420

ttnacnaaaa attttnaaca gtntaaattg ggtttnttgn ccctttnngg nggntgtttt 480

ttttttcggg tccgg 495

<210> 52
<211> 81
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

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<222> (65)

<223> May be any nucleic acid

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<222> (71)
<223> May be any nucleic acid

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<222> (75)
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<400> 52
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gagananata natanatata t 81

<210> 53
<211> 305
<212> DNA
<213> Homo sapiens

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<222> (11)
<223> May be any nucleic acid

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<222> (81)
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<223> May be any nucleic acid

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tnatgcagcc ccagggtttt nttaatgctc aaatggtcgc ccaacgcagc agagagctgc 120

taagtcatca cttccgacaa cagagggtgg ctataatgat gcagcagcag cagcagcagc 180

aacagcagca gcagcagcag cagcagcagc aacagcaaca gcaacagcaa cagcagcaac 240

agcagcaaac ccaggncttc agcccacctc ctaatgtgac tgcttcccnc agcatggatg 300

ggctt 305

<210> 54
<211> 307
<212> DNA
<213> Hepatitis C virus

<220>
<221> UNSURE
<222> (212)
<223> May be any nucleic acid

<400> 54
tggggtgtga agctccggtg ctggtgcggc gggggactgc ggggccagcc tcagtttaaa 60

ccccctcagc agtctttctg tcgttgccct ccacactgcg agactctgga gggcgatctg 120

gaggtctgga agataaccga ttcctgggag atttgggggt agtctccaat ctgtccctgg 180

ctcatcttgt gacccgaagc cggcggcctt gncaggagta ttctagaatg agtgcacata 240

aaaatacctt caaacggtag cagcagcagc agcagcagca gcagcaagca gcagcagcag 300

cagcagc 307

<210> 55
<211> 88
<212> DNA
<213> Unknown

<220>
<221> UNSURE
<222> (6)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (7)
<223> May be any nucleic acid

<220>
<221> UNSURE

<222> (78)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (83)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (87)
<223> May be any nucleic acid

<220>
<223> Description of Unknown Organism:Unknown

<400> 55
ggacanngac tactctctct ctctctctct ctctctctgc tgctgctgct gtgctgctgc 60

tgctgctgct gctgccgntg tgngcana 88

<210> 56
<211> 346
<212> DNA
<213> Unknown

<220>
<221> UNSURE
<222> (278)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (288)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (299)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (313)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (342)
<223> May be any nucleic acid

<220>
<223> Description of Unknown Organism:Unknown

<400> 56
ggcacagccc aactggtgat gctgctgctg ctgctgctgc tgccgccgcc gcctctattg 60

ctgatactct agtggggctg gaagggtggt tcctattcgc accatcgcca accagagaca 120

gagggaaaaa aaaaaccggc agccactgct gaatgttggg ttcggaggct gcatccgact 180

cggtcacaag gaaaatggat tcagtttgca tctctccctc ctttaaacag cttctccggg 240

tctcagcatg ggcttccagg gcagcgattg aggagacntt accaaggngc accacacant 300

agatgctgag acntcgtgac tccaggataa gaaacattaa cngggg 346

<210> 57
<211> 496
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<220>
<221> UNSURE
<222> (11)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (78)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (195)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (197)
<223> May be any nucleic acid

<220>
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<222> (286)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (291)
<223> May be any nucleic acid

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<221> UNSURE
<222> (293)
<223> May be any nucleic acid

<220>
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<222> (315)
<223> May be any nucleic acid

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<222> (328)
<223> May be any nucleic acid

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<221> UNSURE
<222> (329)
<223> May be any nucleic acid

<220>
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<222> (344)
<223> May be any nucleic acid

<220>
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<222> (346)
<223> May be any nucleic acid

<220>
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<222> (352)
<223> May be any nucleic acid

<220>
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<222> (354)
<223> May be any nucleic acid

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<222> (358)
<223> May be any nucleic acid

<220>
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<222> (366)
<223> May be any nucleic acid

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<223> May be any nucleic acid

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<222> (406)
<223> May be any nucleic acid

<220>
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<222> (410)
<223> May be any nucleic acid

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<222> (418)
<223> May be any nucleic acid

<220>
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<223> May be any nucleic acid

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<223> May be any nucleic acid

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<222> (443)
<223> May be any nucleic acid

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<223> May be any nucleic acid

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<222> (454)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (459)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (471)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (473)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (474)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (481)
<223> May be any nucleic acid

<400> 57
gaattcggca naggtgcaca gatgtggtgg atggggaggg ccgcacggga cagaagttct 60

ccctgtgtat tctgacgnct gagaaaggag catttcatcc gggcggagac caaggagatc 120

gtcaatgggt ggctggagat gctcatggtc tatccccgga ccaacaagca gaatcagaag 180

aagaaacgga aagtngnagc cccccacacc acaggagcct gggactgcca agttgggctg 240

ttaccagcag cagcagcagc agcagcagca gcagcagcat ccccantgct ntnggaaagt 300

tcccaccacc aagtnccaca atttgggnna aaaccaaggt tgtngnagac gngntttngg 360

gatttnggca ttgtgggttg cttgcatgga aggacattng gttgtnggtn ccttggangn 420

tacaattacc atttncggtt gtnaaggtta aanntccgnc attcagaagg ntnnaaggtg 480

ntttgaagtc catttg 496

<210> 58
<211> 268
<212> DNA
<213> Drosophila sp.

<220>
<221> UNSURE
<222> (16)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (51)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (60)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (202)
<223> May be any nucleic acid

<400> 58
aacacttatc cttganagct ctgtttggga agcaggacaa agctacatgt naggaaactn 60

tggagcctcc gcagactctc caccagcagc agcagcagca gcagcagcag caagagaagc 120

ttccaattag gcaggggggtt gtacgctccc tgtcctatga ggaacccaga agacactcac 180

cccccattga gaagcagctc tntccagcca ttcagaaact catggtcagg agcgcagacc 240

tccacccatt gtcagagctg cctgaaaa 268

<210> 59
<211> 471
<212> DNA
<213> Homo sapiens

<220>
<221> UNSURE
<222> (249)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (386)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (449)
<223> May be any nucleic acid

<400> 59
tcgacccacg cgtccgctga ggaacagacg ttccctggcg gccctggcgc cttcaaaccc 60

agacatgctg ctgctgctgc tgctgctgcc cctgctctgg gggacaaagg ggatggaggg 120

agacagacaa tatggggatg gttacttgct gcaagtgcag gagctggtga cggtgcagga 180

gggcctgtgt gtccatgtgc cctgctcctt ctcctacccc caggatggct ggactgactc 240

tgacccagnt catggctact ggttccgggc aggagacaga ccataccaag acgctccagt 300

ggccacaaac aacccagaca gagaagtgca ggcagagacc cagggccgat tccaactcct 360

tggggacatt tggagcaacg actgcnccct gagcatcaga gacgccagga agagggataa 420

ggggtcatat ttctttcggc tagagagang aagcatgaaa tggagttaca a 471

<210> 60
<211> 379
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<220>
<221> UNSURE
<222> (2)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (14)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (31)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (135)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (315)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (332)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (349)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (357)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (374)
<223> May be any nucleic acid

<400> 60
anttcggcan aggnaaggga gagggtgacc ngcatcccaa ctagatttca gtggagtgaa 60

gttcaggagg catggagctg acaaccatga ggcctcggca gccaccgcca ccaccgccgc 120

cgccaccacc gtagncagca gcagcagcag cagcagcagc aagagttaac tctgacttag 180

ggaatagaga cagccagaga gaaatgtgat caatgaagga gacatctgga gtgtgcgtgc 240

ttcttcagag gggacgggtg atgggcagat ttggaaaaag caccgcagat tgggaacctt 300

atcttttctt tttcntaaaa ttgttgttat gnaaatttgg gtttttccng taacttntta 360

aaaacttaaa agtnggttt 379

<210> 61
<211> 255
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<220>
<221> UNSURE
<222> (121)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (183)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (254)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (255)
<223> May be any nucleic acid

<400> 61
aattccgaca atggaaagca ctcttagcct tgcagtggtc tacattttta aggaaccaat 60

atttcagcat tctttattac ccggcacgct gtgtcctttg tcagagttca agtttatggt 120

nactgccagg gtcagacagt ccatttgctg ctgctgctgc tgctgctgct ttctcgaact 180

ggnatggcat tagggaagct gctgtctgag tgttagggaa tgtcttggct aagtaaagcc 240

aatgttcttt cctnn 255

<210> 62
<211> 5289
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<400> 62
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ctatcccgtc gctgcgccct tgtcgccggc cccggccgct gcatccgcgt ccgcacaggc 120

tccttgctgg gcacaaatag ctccaccatg gggctggcct ggggactcgg tgtcctgctc 180

ctgttgcatg cctgcggctc caaccgcatt ccagagtctg ggggagacaa cagtgtgttt 240

gacatctttg aactcaccgg agctgcccgc aagcggtctg ggcgccgact ggtgaagggc 300

cctgaccctt ctagcccagc tttccgcatc gaggatgcca acctgatccc ccctgtgcct 360

gacaagaagt tccaagacct agtggatgct gtgcgggcgg agaaaggttt cctcctcctg 420

gcctccctga ggcaaatgaa gaagacccgg ggtaccctgc tggctgtgga gcggaaagac 480

cactctggcc aggtcttcag cgtgatctcc aatggcaagg cgggcaccct ggacctgagc 540

ctgaccgtgc aggggaagca gcatgtggtg tcggtggaag aagcactcct ggcgactggc 600

cagtggaaga gcatcaccct gtttgtgcag gaggacaggg cccagctgta catcgactgt 660

gagaagatgg agaatgcgga gctggatgtc cccatccaga gcatcttcac cagggacctg 720

gccagcatcg ccaggctccg cattgccaaa ggaggtgtca acgacaattt ccaggggggtg 780

ctgcagaatg taaggtttgt ctttggaacc acaccagaag acatcctcag gaacaaaggc 840

tgctccagct ctaccagtgt ctttgtcacc cttgacaaca acgtggtgaa tgggtccagc 900

cctgccatcc gcaccgacta cattggccac aagacaaagg acctgcaagc catctgtggc 960

atctcatgtg acgagctgtc cagcatggtc ctggagctca ggggtctacg caccatcgtg 1020

accacgctgc aggacagtat ccgcaaagtg accgaagaga acaaagagct ggccaacgag 1080

ctgaggaggc ccccactctg ctaccacaac ggagtgcagt acaggactgg cgacgagtgg 1140

acggtggaca gctgcactga gtgtcgctgc cagaactcag ttaccatctg caaaaaagtg 1200

tcctgtccca tcatgccctg ctccaatgcc acagttccgg atggagaatg ctgcccacgg 1260

tgctggccca gcgactctgc agacgatggc tggtccccgt ggtctgagtg gacctcttgc 1320

tctgtgacct gtggcaatgg aatccagcag cgtggccgct cctgcgacag cctcaacaac 1380

agatgcgagg gctcctctgt gcagacgcgg acctgccaca tccaggagtg tgacaagaga 1440

tttaaacagg atggcggctg gagccactgg tccccatggt catcttgctc cgtaacatgt 1500

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gttggtgatg tgacagaaaa ccagatctgc aacaagcagg actgtcccat tgacggatgc 1800

ctgtccaatc cctgctttgc tggtgtccag tgtaccagct accctgatgg cagctggaag 1860

tgtggtgcct gtcccccagg ctatagtgga gatggagtcg agtgcaaaga cgttgatgag 1920

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gaccccggct acaactgcct gccctgccca ccgcgcttca ctggctcgca gccctttggc 2040

cggggcgtgg aacatgccac cgccaacaag caggtatgca agccccgaaa cccctgcaca 2100

gacgggacac acgactgcaa caagaacgcc aagtgcaact acctgggcca ctacagcgac 2160

cccatgtacc gctgcgagtg caagcctggc tacgccggca acggcatcat ctgcggggag 2220

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gacaactgtc cattccatta caacccagcc cagtacgact atgacagaga tgacgtggga 2460

gaccgctgtg acaactgccc ctacaaccac aacccagacc aggctgacac agataacaat 2520

ggggaaggag acgcctgtgc agctgacatt gatggggaca gtatcctcaa tgaacgggac 2580

aactgccagt atgtctacaa tgtggaccag aaagacactg acatggacgg ggttggtgat 2640

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atcagtgaga ctgatttccg ccgattccag atgattcctc tagatcccaa agggacatcc 3060

cagaatgacc ctaactgggt tgtacgccat cagggtaaag aactcgtcca gactgtcaac 3120

tgtgaccctg gacttgctgt aggttatgac gaatttaacg ccgtggactt cagtggcacc 3180

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cccacgaggg ctcaggggta ctctggactt tccgtgaagg ttgtaaactc caccacgggg 3360

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gtcttctctc aagaaatggt gttcttctcc gacctgaaat atgaatgcag agactcctaa 3660

tcatcaaact gttgatcaaa agactgatca taaaccaatg ctggtattgc accttctgga 3720

accatgggct tagaaaaccc ccaggatcgc gcctcgctgc ctgcctttgc tctctgcttg 3780

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gaccctgcat tcagcctctg actgagaaga atcttccaag gagacaaaca atgactttgg 3900

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taacccacat aaataggcac ttaaatagga gcagggaagg aaggaaaaga ctggcttctg 4320

gacttcctcc cagatttcca ccccttaaca catcacctgt agtgaccaga acagggagtc 4380

ggagttaaac cgacacaagg cagggccagc tgctgcagct tggttctatt gaaattgtca 4440

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ggaagaagcg taaggactat ccatatcatc tttgctacaa gtcattatga ctgtaagatt 4800

gtaaatacag attatttatt aactctgttc tacctggaat ctagtttcat atggaaagtg 4860

tttgagagca ggtagttgag atcgatcagc aaatctttca caggaatggc acaaggaaac 4920

cagcatagca agctgctctt caccttgtgc ttagactgga tgatttggaa ttctttttttc 4980

ctttttttttc ccaagtggaa ttacttggtt gtccatttgc aagtgttttt agtttgcaaa 5040

gaaagccaag aggccattaa tactgtctta tcccatccct tgtgcctatt tccagggaga 5100

tgaaaagcat ctacatttat tatttttgcc tttttccaaa agaaaaaaat gacaaaggtg 5160

aaacttgtat acaaatatta cctcatttgt tgtgtgactg agtaaagaat tttgggatca 5220

aacagaaaga gtttaagtgt ctaacaaact taaagctact gtagtaccta aaaaaaaaaa 5280

aaaaaaaaa 5289

<210> 63
<211> 2053
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<400> 63
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ccacggcctc caccccgcgc ctctccagcg ctctatcccg tcgctgcgcc cttgtcgccg 120

gccccggcgc tgcatccgcg tccgcacagg ctccttgact gggcacaaat agctccacca 180

tggggctggc ctggggactc ggtgtcctgc tcctgttgca tgcctgcggc tccaaccgca 240

ttccagagtc tgggggagac aacagtgtgt ttgacatctt tgaactcacc ggagctgccc 300

gcaacggtac tgggcgccga ctggtgaagg gccctgaccc ttctagccca gctttccgca 360

tcgaggatgc caacctgatc ccccctgtgc ctgacaagaa gttccaagac ctagtggatg 420

ctgtgcgggc ggagaaaggt ttcctcctcc tggcctccct gaggcaaatg aagaagaccc 480

ggggtaccct gctggctgtg gagcggaaag accactctgg ccaggtcttc agcgtgatct 540

ccaatggcaa ggcgggcacc ctggacctga gcctgaccgt gcaggggaag cagcatgtgg 600

tgtcggtgga agaagcactc ctggcgactg gccagtggaa gagcatcacc ctgtttgtgc 660

aggaggacag ggcccagctg tacatcgact gtgagaagat ggagaatgcg gagctggatg 720

tccccatcca gagcatcttc accagggacc tggccagcat cgccaggctc cgcattgcca 780

aaggaggtgt caacgacaat ttccaggggg tcctgcagaa tgtaaggttt gtctttggaa 840

ccacaccaga agacatcctc aggaacaaag gctgctccag ctctaccagt gtctttgtca 900

cccttgacaa caacgtggtg aatgggtcca gccctgccat ccgcaccgac tacattggcc 960

acaagacaaa ggacctgcaa gccatctgtg gcatctcatg tgacgagctg tccagcatgg 1020

tcctggagct caggggtcta cgcaccatcg tgaccacgct gcaggacagt atccgcaaag 1080

tgaccgaaga gaacaaagag ctggccaacg agctgaggag gcccccactc tgctaccaca 1140

acggagtgca gtacaggact ggcgacgagt ggacggtgga cagctgcact gagtgtcgct 1200

gccagaactc agttaccatc tgcaaaaaag tgtcctgtcc catcatgccc tgctccaatg 1260

ccacagttcc ggatggagaa tgctgcccac ggtgctggcc cagcgactct gcagacgacg 1320

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ctgcaactcc cccagccccc agatgaatgg gaagccatgt gagggcaaag cccgggagac 1620

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<213> Unknown

<220>
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<212> DNA
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<220>
<223> Description of Unknown Organism:Unknown

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<212> DNA
<213> Unknown

<220>
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gcggctcccg cgggggcctc ggtgtgctac tcgtccccgc ccagcgtggg atcggtgcag 480

gagctagctc agcgcgccgc ggtggtgatc gagggaaagg tgcacccgca gcggcggcag 540

caggggcac tcgacaggaa ggcggcggcg gcggcgggcg aggcaggggc gtggggcggc 600

gatcgcgagc cgccagccgc gggcccacgg gcgctggggc cgcccgccga ggagccgctg 660

ctcgccgcca acgggaccgt gccctcttgg cccaccgccc cggtgcccag cgccggcgag 720

cccggggagg aggcgcccta tctggtgaag gtgcaccagg tgtgggcggt gaaagccggg 780

ggcttgaaga aggactcgct gctcaccgtg cgcctgggga cctggggcca ccccgccttc 840

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aacagcacca gccgcgcgcc ggccgccttc cgagcctctt tccccccctct ggagacgggc 960

cggaacctca agaaggaggt cagccgggtg ctgtgcaagc ggtgcgcctt gcctccccaa 1020

ttgaaagaga tgaaaagcca ggaatcggct gcaggttcca aactagtcct tcggtgtgaa 1080

accagttctg aatactcctc tctcagattc aagtggttca agaatgggaa tgaattgaat 1140

cgaaaaaaca aaccacaaaa tatcaagata caaaaaaagc cagggaagtc agaacttcgc 1200

attaacaaag catcactggc tgattctgga gagtatatgt gcaaagtgat cagcaaatta 1260

ggaaatgaca gtgcctctgc caatatcacc atcgtggaat caaacgctac atctacatcc 1320

accactggga caagccatct tgtaaaatgt gcggagaagg agaaaacttt ctgtgtcaat 1380

ggaggggagt gcttcatggt gaaagacctt tcaaacccct cgagatactt gtgcaagtgc 1440

ccaaatgagt ttactggtga tcgctgccaa aactacgtaa tggccagctt ctacagtacg 1500

tccactccct ttctgtctct gcctgaatag gagcatgctc agttggtgct gctttcttgt 1560

tgctgcatct cccctcagat tccacctaga gctagatgtg tcttaccaga tctaatattg 1620

actgcctctg cctgtcgcat gagaacatta acaaaagcaa ttgtattact tcctctgttc 1680

gcgactagtt ggctctgaga tactaatagg tgtgtgaggc tccggatgtt tctggaattg 1740

atattgaatg atgtgataca aattgatagt caatatcaag cagtgaaata tgataataaa 1800

ggcatttcaa agtctcactt ttattgataa aataaaaatc attctactga acagtccatc 1860

ttctttatac aatgaccaca tcctgaaaag ggtgttgcta agctgtaacc gatatgcact 1920

tgaaatgatg gtaagttaat tttgattcag aatgtgttat ttgtcacaaa taaacataat 1980

aaaagg 1986

<210> 72
<211> 2003
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<220>
<221> UNSURE
<222> (31)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (32)
<223> May be any nucleic acid

<400> 72
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tttctgtggt tccatccact tcttcccccc cctcctccca taaacaactc tcctaccct 120

gcacccccaa taaataaata aaaggaggag ggcaaggggg gaggaggagg agtggtgctg 180

cgaggggaag gaaaagggag gcagcgcgag aagagccggg cagagtccga accgacagcc 240

agaagcccgc acgcacctcg caccatgaga tggcgacgcg ccccgcgccg ctccgggcgt 300

cccggccccc gggcccagcg ccccggctcc gccgcccgct cgtcgccgcc gctgccgctg 360

ctgccactac tgctgctgct ggggaccgcg gccctggcgc cgggggcggc ggccggcaac 420

gaggcggctc ccgcgggggc ctcggtgtgc tactcgtccc cgcccagcgt gggatcggtg 480

caggagctag ctcagcgcgc cgcggtggtg atcgagggaa aggtgcaccc gcagcggcgg 540

cagcaggggg cactcgacag gaaggcggcg gcggcggcgg gcgaggcagg ggcgtggggc 600

ggcgatcgcg agccgccagc cgcgggccca cgggcgctgg ggccgcccgc cgaggagccg 660

ctgctcgccg ccaacgggac cgtgccctct tggcccaccg ccccggtgcc cagcgccggc 720

gagcccgggg aggaggcgcc ctatctggtg aaggtgcacc aggtgtgggc ggtgaaagcc 780

gggggcttga agaaggactc gctgctcacc gtgcgcctgg ggacctgggg ccaccccgcc 840

ttcccctcct gcgggaggct caaggaggac agcaggtaca tcttcttcat ggagcccgac 900

gccaacagca ccagccgcgc gccggccgcc ttccgagcct ctttcccccc tctggagacg 960

ggccggaacc tcaagaagga ggtcagccgg gtgctgtgca agcggtgcgc cttgcctccc 1020

caattgaaag agatgaaaag ccaggaatcg gctgcaggtt ccaaactagt ccttcggtgt 1080

gaaaccagtt ctgaatactc ctctctcaga ttcaagtggt tcaagaatgg gaatgaattg 1140

aatcgaaaaa acaaaccaca aaatatcaag atacaaaaaa agccagggaa gtcagaactt 1200

cgcattaaca aagcatcact ggctgattct ggagagtata tgtgcaaagt gatcagcaaa 1260

ttaggaaatg acagtgcctc tgccaatatc accatcgtgg aatcaaacgc tacatctaca 1320

tccaccactg ggacaagcca tcttgtaaaa tgtgcggaga aggagaaaac tttctgtgtg 1380

aatggagggg agtgcttcat ggtgaaagac ctttcaaacc cctcgagata cttgtgcaag 1440

tgcccaaatg agtttactgg tgatcgctgc caaaactacg taatggccag cttctacagt 1500

acgtccactc cctttctgtc tctgcctgaa taggagcatg ctcagttggt gctgctttct 1560

tgttgctgca tctcccctca gattccacct agagctagat gtgtcttacc agatctaata 1620

ttgactgcct ctgcctgtcg catgagaaca ttaacaaaag caattgtatt acttcctctg 1680

ttcgcgacta gttggctctg agatactaat aggtgtgtga ggctccggat gtttctggaa 1740

ttgatattga atgatgtgat acaaattgat agtcaatatc aagcagtgaa atatgataat 1800

aaaggcattt caaagtctca cttttattga taaaataaaa atcattctac tgaacagtcc 1860

atcttcttta tacaatgacc acatcctgaa aagggtgttg ctaagctgta accgatatgc 1920

acttgaaatg atggtaagtt aattttgatt cagaatgtgt tatttgtcac aaataaacat 1980

aataaaagga aaaaaaaaaa aaa 2003

<210> 73
<211> 957
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<220>
<221> UNSURE
<222> (809)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (810)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (811)
<223> May be any nucleic acid

<400> 73
tctcgcccca acttttccc ccgcgctccg cagcagcagc agcagcagca gcagcagcag 60

caaaatggca gacctcttca gcggactcgt gggcggcgtc gtcggcgctg ttgctgcagc 120

agatttgcct gcggagggcg agagggcccc ccgccccgcc cccggcactg cctggacttg 180

ctgctgcagc aaactgcaag aaggggcccg cgagctggag ggttttgtgc agcagctgag 240

ttttgttgca gggaagctgg cctgctgcct gcgggtgggg gcggagcagc tggcgcgctg 300

cgctgcggag gggcggctgc ccagcagcag cagcagcagc agctgctgcg cgctgctgca 360

gctcgagaag caggacctcg agcagagcct cgaggccggc aagcagggcg cggagtgcct 420

cttgaggagc agcaaactgg ccctcgaggc cctcctcgag ggggcccgcg ttgcagcaac 480

gcggggtttg ctgctggtcg agagcagcaa agacacggtg ctgcgcagca ttccccacac 540

ccaggagaag ctggcccagg cctacagttc tttcctgcgg ggctaccagg gggcagcagc 600

ggggaggtct ctgggctacg gggcccctgc tgctgcttac ggccagcagc agcagcccag 660

cagctacggg gcgccccccg cctccagcca gcagccctcc ggcttcttct ggtagccctg 720

cagcagcagc agcagcagca gcagcagcag cagcgcgggc ggcagccgcg gcggggccgg 780

ggcgccgctg cagcaacagc agcagccgnn ncggctagcg ccgcggagca ctcgcaggga 840

actccacagg cagcgggaga gcagcaggga cgagaagcag gtcatgtagc gcaggcagca 900

gcgccagctg cagcagcagc agcagcagca gcagcagcag cagcagctcc tgcaccg 957

<210> 74
<211> 957
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<220>
<221> UNSURE
<222> (809)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (810)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (811)
<223> May be any nucleic acid

<400> 74
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caaaatggca gacctcttca gcggactcgt gggcggcgtc gtcggcgctg ttgctgcagc 120

agatttgcct gcggagggcg agagggcccc ccgccccgcc cccggcactg cctggacttg 180

ctgctgcagc aaactgcaag aaggggcccg cgagctggag ggttttgtgc agcagctgag 240

ttttgttgca gggaagctgg cctgctgcct gcgggtgggg gcggagcagc tggcgcgctg 300

cgctgcggag gggcggctgc ccagcagcag cagcagcagc agctgctgcg cgctgctgca 360

gctcgagaag caggacctcg agcagagcct cgaggccggc aagcagggcg cggagtgcct 420

cttgaggagc agcaaactgg ccctcgaggc cctcctcgag ggggcccgcg ttgcagcaac 480

gcggggtttg ctgctggtcg agagcagcaa agacacggtg ctgcgcagca ttccccacac 540

ccaggagaag ctggcccagg cctacagttc tttcctccgg ggctaccagg gggcagcagc 600

ggggaggtct ctgggctacg gggcccctgc tgctgcttac ggccagcagc agcagcccag 660

cagctacggg gcgcccccgg cctccagcca gcagccctcc ggcttcttct ggtagccctg 720

cagcagcagc agcagcagca gcagcagcag cagcgcgggc ggcagccgcg gcggggccgg 780

ggcgccgctg cagcaacagc agcagccgnn ncggctagcg ccgcggagca ctcgcaggga 840

actccacagg cagcgggaga gcagcaggga cgagaagcag gtcatgtagc gcaggcagca 900

gcgccagctg cagcagcagc agcagcagca gcagcagcag cagcagctcc tgcaccg 957

<210> 75
<211> 1089
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<220>
<221> UNSURE
<222> (376)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (377)
<223> May be any nucleic acid

<220>
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<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (848)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (849)
<223> May be any nucleic acid

<220>
<221> UNSURE
<222> (850)
<223> May be any nucleic acid

<400> 75
gaattccctc caactcttcg cgactctctc tctctcgccc caacttttc ccccgcgccc 60

cgcagcagca gcagcagcag cagcagcaaa atggcagacc tcttcagcgg actcgtgggc 120

ggcgtcgtcg gcgctgttgc tgcagcagat ttgcctgcgg agggcgagag ggcccccccgc 180

cccgcccccg gcactgcctg gacttgctgc tgcagcaaac tgcaagaagg ggcccgcgag 240

ctggagggtt ttctgcagca gctgagtttt gttgcaggga agctggcctg ctgcctgcgg 300

gtgggggcgg agcagctggc gcgctgcgct gcggaggggc ggctgcccag cagcagcagc 360

agcagcagct gctgcnngct gctgcagctc gagaagcagg acctcgagca gagcctcgag 420

gccggcaagc agggcgcgga gtgcctcttg aggagcagca aactggccct cgaggccctc 480

ctcgaggggg cccgcgttgc agcaacgcgg ggtttgctgc tggtcgagag cagcaaagac 540

acggtgctgc gcagcattcc ccacacccag gagaagctgg ctcaggccta cagttctttc 600

ctgcggggct accaggggggc agcagcgggg aggtctctgg gctacggggc ccctgctgct 660

gcttacggcc agcagcagca gcccagcagc tacggggcgc cccccgcctc cagccagcag 720

ccctccggct tcttctggta gccctgcagc agcagcagca gcagcagcag cagcagcagc 780

ggcggcggca gccgcggcgg ggccgggggcg ccgctgcagc aacagcagca gccgcggcgg 840

ctagcgnnnn gagcactcgc agggaactcc acaggcagcg ggagagcagc agggacgaga 900

agcaggtcta tgtagcgcag gcagcagcgc cagctgcagc agcagcagca gcagcagcag 960

cagcagcagc agctcctgca ccgcagcgtt gtgtcattta ttacgttggc agctctgagg 1020

cctcggcgca gccaacgcgc ctcaggtatc tttcagactc ttttctctaa ggtcttccag 1080

acggaattc 1089

<210> 76
<211> 1985
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<400> 76
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ctcccaccgg cctgcccttc cccgcgggac tatcgccccc acgtttccct cagccctttt 120

ctctcccggc cgagccgcgg cggcagcagc agcagcagca gcagcaggag gaggagcccg 180

gtggcggcgg tggccgggga gcccatggcg tacagtcaag gaggcggcaa aaaaaaagtc 240

tgctactact acgacggtga tattggaaat tattattatg gacagggtca tcccatgaag 300

cctcatagaa tccgcatgac ccataacttg ctgttaaatt atggcttata cagaaaaatg 360

gaaatatata ggccccataa agccactgcc gaagaaatga caaaatatca cagtgatgag 420

tatatcaaat ttctacggtc aataagacca gataacatgt ctgagtatag taagcagatg 480

catatattta atgttggaga agattgtcca gcgtttgatg gactctttga gttttgtcag 540

ctctcaactg gcggttcagt tgctggagct gtgaagttaa accgacaaca gactgatatg 600

gctgttaatt gggctggagg attacatcat gctaagaaat acgaagcatc aggattctgt 660

tacgttaatg atattgtgct tgccatcctt gaattactaa agtatcatca gagagtctta 720

tatattgata tagatattca tcatggtgat ggtgttgaag aagcttttta tacaacagat 780

cgtgtaatga cggtatcatt ccataaatat ggggaatact ttcctggcac aggagacttg 840

agggatattg gtgctggaaa aggcaaatac tatgctgtca attttccaat gtgtgatggt 900

atagatgatg agtcatatgg gcagatattt aagcctatta tctcaaaggt gatggagatg 960

tatcaaccta gtgctgtggt attacagtgt ggtgcagact cattatctgg tgatagactg 1020

ggttgtttca atctaacagt caaaggtcat gctaaatgtg tagaagttgt aaaaactttt 1080

aacttaccat tactgatgct tggaggaggt ggctacacaa tccgtaatgt tgctcgatgt 1140

tggacatatg agactgcagt tgcccttgat tgtgagattc ccaatgagtt gccatataat 1200

gattactttg agtattttgg accagacttc aaactgcata ttagtccttc aaacatgaca 1260

aaccagaaca ctccagaata tatggaaaag ataaaacagc gtttgtttga aaatttgcgc 1320

atgttacctc atgcacctgg tgtccagatg caagctattc cagaagatgc tgttcatgaa 1380

gacagtggag atgaagatgg agaagatcca gacaagagaa tttctattcg agcatcagac 1440

aagcggatag cttgtgatga agaattctca gattctgagg atgaaggaga aggaggtcga 1500

agaaatgtgg ctgatcataa gaaaggagca aagaaagcta gaattgaaga agataagaaa 1560

gaaacagagg acaaaaaaac agacgttaag gaagaagata aatccaagga caacagtggt 1620

gaaaaaacag ataccaaagg aaccaaatca gaacagctca gcaacccctg aatttgacag 1680

tctcaccaat ttcagaaaat cattaaaaag aaaatattga aaggaaaatg ttttcttttt 1740

gaagacttct ggcttcattt tatactactt tggcatggac tgtatttatt ttcaaatggg 1800

actttttcgt ttttgttttt ctgggcaagt tttattgtga gattttctaa ttatgaagca 1860

aaatttcttt tctccaccat gctttatgtg atagtattta aaattgatgt gagttattat 1920

gtcaaaaaaa ctgatctatt aaagaagtaa ttggcctttc tgagctgaaa aaaaaaaaaa 1980

aaaag 1985

<210> 77
<211> 476
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:Unknown

<400> 77
ccaccctcct ccccctcccc cggccacttc gctaacttgg tggctgttgt gatgcgtatt 60

cctgtagatc cgagcaccag ccggcgcttc agccccccct ccagcagcct gcagcccggc 120

aaaatgagcg acgtgagccc ggtggtggct gcgcaacagc agcagcaaca gcagcagcag 180

caacagcagc agcagcagca gcaacagcag cagcagcagc aggaggcggc ggcggcggct 240

gcggcggcag cggcggctgc ggcggcggca gctgcagtgc cccggttgcg gccgccccac 300

gacaaccgca ccatggtgga gatcatcgcc gaccacccgg ccgaactcgt ccgcaccgac 360

agccccaact tcctgtgctc ggtgctgccc tcgcactggc gctgcaacaa gaccctgccc 420

gtggccttca aggtaagagg ctaccccgcc ccccgccccc ggccgggagc ggcgga 476

<210> 78
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:DNA Primer

<400> 78
gcattttgga tccgcctttt catg 24

<210> 79
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:DNA Primer

<400> 79
gttgtgtgct gcagattgtt cc 22

<210> 80
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:DNA Primer

<400> 80
gaaaaatggg gatccgaggt g 21

<210> 81
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:DNA Primer

<400> 81
gcaggagaat tccgtccatg 20

<210> 82
<211> 5
<212> PRT
<213> Homo sapiens

<220>
<221> UNSURE
<222> (3)
<223> Can be any amino acid

<400> 82
Trp Ser Xaa Trp Ser
1 5

<210> 83
<211> 6
<212> PRT
<213> Homo sapiens

<400> 83
Cys Ser Val Thr Cys Gly
1 5

<210> 84
<211> 5
<212> PRT
<213> Homo sapiens

<220>
<221> UNSURE
<222> (4)
<223> Can be any amino acid

<400> 84
Gly Cys Gln Xaa Arg
1 5

<210> 85
<211> 733
<212> DNA
<213> Homo sapiens

<400> 85
gggatccgga gcccaaatct tctgacaaaa ctcacacatg cccaccgtgc ccagcacctg 60

aattcgaggg tgcaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 120

tctcccggac tcctgaggtc acatgcgtgg tggtggacgt aagccacgaa gaccctgagg 180

tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 240

aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 300

ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca acccccatcg 360

agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 420

catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 480

atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 540

ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag ctcaccgtgg 600

acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 660

acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgagtg cgacggccgc 720

gactctagag gat 733

<210> 86
<211> 86
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:DNA Primer

<400> 86
gcgcctcgag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc 60

cccgaaatat ctgccatctc aattag 86

<210> 87
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:DNA Primer

<400> 87
gcggcaagct ttttgcaaag cctaggc 27

<210> 88
<211> 271
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR Fragment

<400> 88
ctcgagattt ccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg 60

aaatatctgc catctcaatt agtcagcaac catagtcccg cccctaactc cgcccatccc 120

gcccctaact ccgcccagtt ccgcccattc tccgccccat ggctgactaa ttttttttat 180

ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt 240

ttttggaggc ctaggctttt gcaaaaagct t 271

<210> 89

<211> 32
<212> DNA
<213> Homo sapiens

<400> 89
gcgctcgagg gatgacagcg atagaacccc gg 32

<210> 90
<211> 31
<212> DNA
<213> Homo sapiens

<400> 90
gcgaagcttc gcgactcccc ggatccgcct c 31

<210> 91
<211> 12
<212> DNA
<213> Homo sapiens

<400> 91
ggggactttc cc 12

<210> 92
<211> 73
<212> DNA
<213> Homo sapiens

<400> 92
gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg 60

ccatctcaat tag 73

<210> 93
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR Fragment

<400> 93
gcggcaagct ttttgcaaag cctaggc 27